Evaluation of Silk and Rose Biomaterials in the Nano-Cosmeceutical Industry: the Claiming Balance Between Nature, Science, and Regulation

Evaluation of Silk and Rose Biomaterials In the Nano-Cosmeceutical Industry:

The Claiming Balance Between Nature, Science, and Regulation

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Abstract

Human beings are constantly trying to find the next way to sustain youth and vitality with new creams, pills, and supplements – it is no wonder the cosmeceutical industry is one of the fastest growing segments of the personal care industry. Trending anti-aging nanotechnology derived ingredients such as the infusion of collagen, hyaluronic acid, resveratrol, honey, coconut oil, and silk therapeutic treatment are but a small part of the vast explosion in the lucrative "skinceutical" market. Alternative application utilizing more natural materials in combination with varying medicinal therapies is certainly gaining momentum partnering both science and naturopath dualities. This approach is the deliberate utilization of extracting a chemical component from a natural biomaterial and applying it to all facets of the body for beneficial therapeutic purposes.

The purpose of this thesis was to examine the historical development of the cosmeceutical industry (more specifically the resultant nano-cosmeceutical industry formation) and the use of biomaterials for skincare and its beautifying benefits – focusing on the anti-aging phenomenon. We aimed to provide an overview of the developing trend in nanotechnology (i.e. silk protein nanoparticle) in collaboration with natural biomaterials (i.e. essential oils) and its synergistic effect. We also examined whether there was substantial evidence that nanoparticles and nanotechnology processes (such as silk protein encapsulation) coupled with essential oils (such as rosehip oil) truly provided improved skincare results. The study focused on providing a thorough comparison on

two specific biomaterial entities (silk protein nanoparticles and rosehip oil) relative to claims substantiated by the cosmeceutical industry with respect to (extrinsic) aging. We collected and reviewed ingredient lists of products branded with claims providing anti-aging results composed of "antioxidant" materials and dissected how it was relevant to the product's identity, function, and performance.

We aimed at curating a diverse range of information from thirteen products drawn from companies (ranging in size) with respect to rosehip, silk, and combination based materials. We summarized the current governing standard applicable to the nano-cosmeceutical industry and provided guidance to bridge any deficiencies utilizing existing federal regulatory agencies. Finally, we reviewed newly structured organizations and Third Party certifications provided direction and assistance toward future nano-cosmeceutical development with respect to claim substantiation. Due to the extensive nature of our data collection while cross-referenced with the current and often ambiguous regulatory landscape – our work was novel in providing a recommended matrix and regulatory guideline for the cosmeceutical industry relative to product claims.

Dedication

I dedicate my graduate thesis work to my family and friends, who have provided love and support throughout my life. There were numerous people who have walked alongside me and offered infinite pieces of insight throughout my career and life - some have placed wonderous opportunities before me, guided me, believed in me, and some simply pushed me gently toward certain life goals. I would not be the individual that I am today without them.

Most importantly, I would like to express my deepest love and respect to my wonderful parents and brother. They have always championed and encouraged all my life endeavors – and with whom have always inspired me with their constant wisdom, strong work ethic, and compassion.

Acknowledgments

I would like to start by expressing my sincere gratitude to my mentor, Dr. Sujata Bhatia, for her endless support and guidance throughout my thesis process. Serving as my Thesis Director, Dr. Bhatia provided continual wisdom and with whom this thesis would not have taken place. Her unwavering enthusiasm helped drive the creative research process – to look beyond the boundaries of atypical work and broaden the scope of the thesis brainstorming process. I consider myself fortunate to have had her as my mentor. She is inspirational in her work to motivate female professionals toward greater things – a pillar of the scientific community.

I would also like to thank Dr. Steven Denkin who served as my Research Advisor of the Biotechnology program. His guidance and encouragement helped fuel the beginnings of my thesis proposal formulation to its completion as a research product. I will never forget meeting with Dr. Denkin to discuss the initial thesis process – both his kindness and motivating spirit were inspiring throughout the entire process. He never stopped believing that I would complete both my thesis work while maintaining a full-time work schedule – I will always be indebted to his nurturing vision.

It was certainly an honor for me to have had the privilege to work and be mentored by such accomplished scientists and educators, as Dr. Bhatia and Dr. Denkin.

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Chapter I

Introduction

Back to Basics

As the average lifespan of mankind continues to lengthen due to improved environmental conditions, advanced medical remedies, continual research in life-threatening diseases, improved solutions to drug treatment using nanotechnology, and a better understanding of health/nutrition – the desire to elongate youthful appearance continues to drive a multi-billion dollar industry.

The demand for the next magic skin care bullet has driven cosmetic companies to amplify their focus and investments into research and development – more specifically investing in examining the synergy between natural biomaterials and nanotechnology advancement. Consequently, it is a fascinating time at the burgeoning cusp of nanotechnology – examining naturally derived biomaterials, which can be chemically extracted and amplified for biomedical applications and research. In fact, an online survey conducted by Harris Poll and commissioned by Kari Gran (of Kari Gran Beauty) found that "59 percent of women over the age of 35 believe buying green beauty is important to them, while an even larger percentage - 73 to be exact - of millennial women seek out cleaner, all-natural products" ("Green Beauty Barometer Survey," 2016). The survey polled 1,126 U.S. women (ages 18 and older) from August 9-11 in 2016 and

evaluated beauty categories such as skin care, hair care, makeup, sunscreen, fragrance and nail care.

Recent studies have seen a surge in improving traditional therapeutic medicinal treatments with naturally derived biomaterials – providing promising results with minimal toxicity, decreased side effects, and enhanced desired product delivery. For example, the restoring properties of essential oils such as rosehip seed oil (*rosa rubiginosa*) – extracted from seeds of the rosa canina shrub (Ilyasoğlu, 2014).

Aging

Whether it is the Fountain of Youth or the pharmaceutical "magic bullet," throughout history, humankind has always sought to obtain the secret to eternal youth. Therefore, it is this preservation of youth that undoubtedly fuels a rapidly growing multi-billion dollar cosmetic and biotechnology industry in the United States. While baby boomers rely on creams and cosmetic surgeries to prevent the inevitable signs of aging, future generations may have another option – Mother Nature or more specifically the utilization of biomaterials coupled with modern nanotechnology.

The biology of aging is certainly a complex and multifaceted realm of research. There are various manifestations of aging, which have ultimately increased the overall identification of potential therapeutic targets for improving longevity of life. Researchers often focus on targets affecting the molecular, tissue, and systemic level when evaluating the aging process. These three targets are exposed to deteriorative effects of various

attributes including oxidative stress and exposure to environmental free radicals, which contribute to productivity decline, memory loss, and the ultimate outcome of aging – death (Chondrogianni et al., 2010).

Yet, how do we define and quantify the aging process as an entity? Generally speaking, researchers have assessed aging as the reduction of epidermal thickness – resulting from decreased cellular renewal rate brought about by two aging factors: extrinsic and intrinsic (Puizina-Ivić, 2008).

Intrinsic aging factors include physiological components and genetic predisposition relative to time while extrinsic aging factors include external influences (such as UV radiation and smoking) (El-Domyati et al., 2002). One of the side effects of natural extrinsically aged skin is the onset of wrinkles, hyperpigmentation, and general loss of elasticity due to external damage over time. A study conducted in 2014 evaluated active ingredients that counteracted changes in the epidermal structure and function – such as antioxidant sources and natural lipid compounds (Lorencini, Brohem, Dieamant, Zanchin, & Maibach, 2014). The review provided several studies which concluded in the significance of preserving hydration with respect to epidermal aging – citing the need for lipids, fatty acid, and antioxidant resources to counteract loss of buoyancy within the dermis layer (refer to Figure 1).

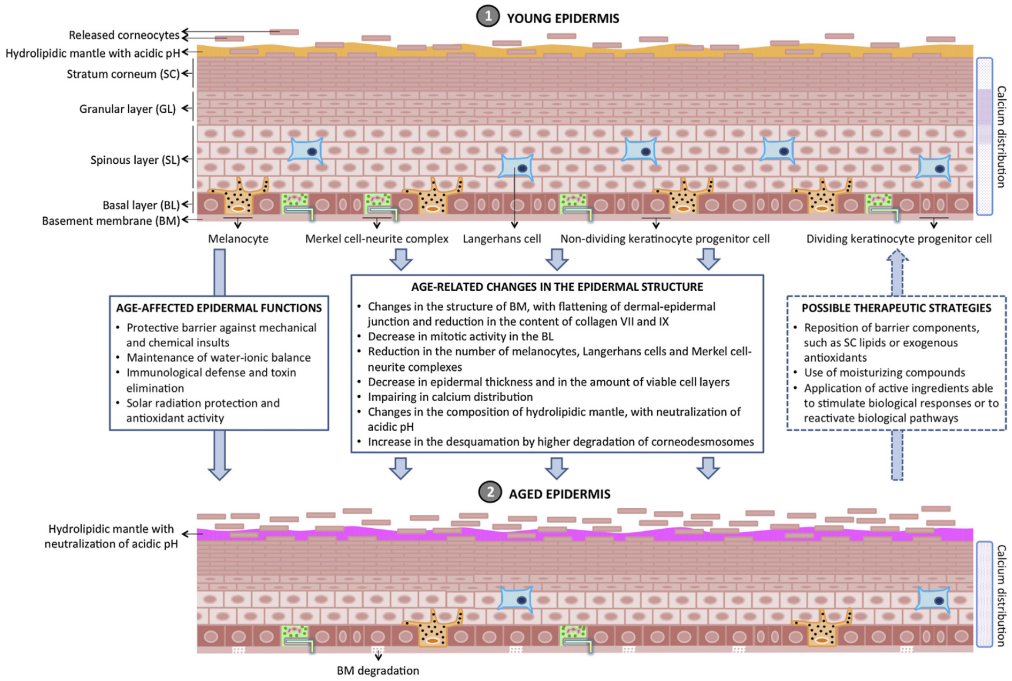


Figure 1. Molecular, cell and morphological changes associated with epidermal aging (Lorencini et al., 2014)

Whether we'd like to admit it or not – skin is certainly a portal in understanding our internal well being as well as physical well being. Therefore, this study focused mainly on extrinsic skin aging relative to skincare products, claims, and regulation.

Drugs (OTC) versus Cosmetics

According to the Food Drug and Cosmetic (FD&C) Act, a drug is defined as 'an article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease – intended to affect the structure or any function of the body" (U.S. Food & Drug Administration, 2012).

Moreover, the FD&C Act further defines a cosmetic as "an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance" (U.S. Food & Drug Administration, 2012). Under the governance of these two statutory laws, there is a clear distinction between what is considered a pharmaceutical or therapeutic drug and what is considered a cosmetic compound. This provided as an effective means of categorizing products for regulatory purposes -- until modern formulating advances introduced a novel concept of combining (cosme)tic and pharma(ceutical) drug components, resulting in cosmeceuticals.

Cosmeceuticals

Oddly enough, under the law, the "cosmeceutical" term itself has no meaning (U.S. Food & Drug Administration, 2012); therefore, regulatory categorization of a cosmeceutical product can be plagued with a myriad of questions. So to delve into understanding the cosmeceutical industry, one certainly has to acknowledge two founding pillars – Raymond Reed and Dr. Albert Kligman. Reed was the founding member of the U.S. Society of Cosmetic Chemists, when he first coined the term "cosmeceutical" while trying to describe the combination of an active ingredient within the realm of cosmetics (Reed, 1962). Reed's initial definition rested on four harmonizing points regarding cosmeceuticals:

1) Whether it is a scientifically designed product intended for external application to

the human body?
2) Whether it produces useful, desired result?
3) Whether it has a desirable aesthetic properties?
4) Whether it meets rigid chemical, physical and medical standards (Reed, 1962)

While in the mid 1990s, Kligman expanded the definition of cosmeceuticals to incorporate prescription strength and medicinal properties (A. Kligman, 2006) - invoking the discussion of whether the cosmetic product provided proven physiological effect mirroring a pharmacologically therapeutic entity. More specifically, Kligman introduced topical products that provided both cosmetic and therapeutic benefits – such as tretinoin, a topical retinoid for the treatment of photo-damage (A. M. Kligman, Grove, Hirose, & Leyden, 1986). Important elements Kligman defined when evaluating cosmeceutical compounds and further assessing its regulatory guidance – is to examine three questions with respect to product claims:

1) Can the active ingredient penetrate the stratum corneum and be delivered in sufficient concentrations to its intended target in the skin over a time course consistent with its mechanism of action?
2) Does the active ingredient have a specific biochemical mechanism of action in the target cell or tissue in human skin?
3) Are there published peer-reviewed, double-blinded, placebo-controlled, statistically significant clinical trials to substantiate the efficacy claims? (D. Kligman, 2000)

The term itself, invoked a myriad of discussion questioning how a defined cosmeceutical product would be regulated, to what degree would such regulation provide, and who would be the subject matter experts to define such guidance. This uncertainty poses many unanswered questions regarding the current autonomy of the unregulated cosmeceuticals industry - fashioning a profitable business marketing unsubstantiated

"science-derived" product claims.

Therefore, with the advent of medical science for cosmetic purposes essentially paving a way for a multi-billion dollar empire – the cultivation of a new type of pharmaceutical and cosmetic hybrid is slowly burgeoning. Yet the term cosmeceuticals is still quite confusing – as it is often marketed incorrectly.

Current Regulations

At present, the pharmaceutical drug industry has a myriad of regulatory guidelines (refer to Table 1) to follow with respect to analytical testing and microbial testing with The International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (International Conference on Harmonisation, 2016) providing very specific (scientific and technical) parameters for recommended validation of assays and compendia organizations like the United States Pharmacopeia (USP) offering standardized methodology for analysis of chemical substances (United States Pharmacopeial, 2016) - all governed through the United States Food & Drug Administration (FDA).

Drug Regulations

In fact, approval of drugs in the United States follows a series of specific steps for New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) (Handoo, Arora, Khera, Nandi, & Sahu, 2012). For the purposes of this study, we will briefly discuss the NDAs approval process as it applies to novel drugs outlined in the following (U.S. Food & Drug Administration, 2015a) (refer to Figure 2 and Figure 3):

1) Preclinical (animal) testing.
2) An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3) Phase 1 studies (typically involve 20 to 80 people).
4) Phase 2 studies (typically involve a few dozen to about 300 people).
5) Phase 3 studies (typically involve several hundred to about 3,000 people).
6) The pre-NDA period, just before a new drug application (NDA) is submitted. A common time for the FDA and drug sponsors to meet.
7) Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8) After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed.
9) If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10) The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug).
11) The FDA's Center for Drug Evaluation and Research (CDER) inspects the facilities where the drug will be manufactured as part of the approval process.
12) FDA reviewers will approve the application or issue a complete response letter.

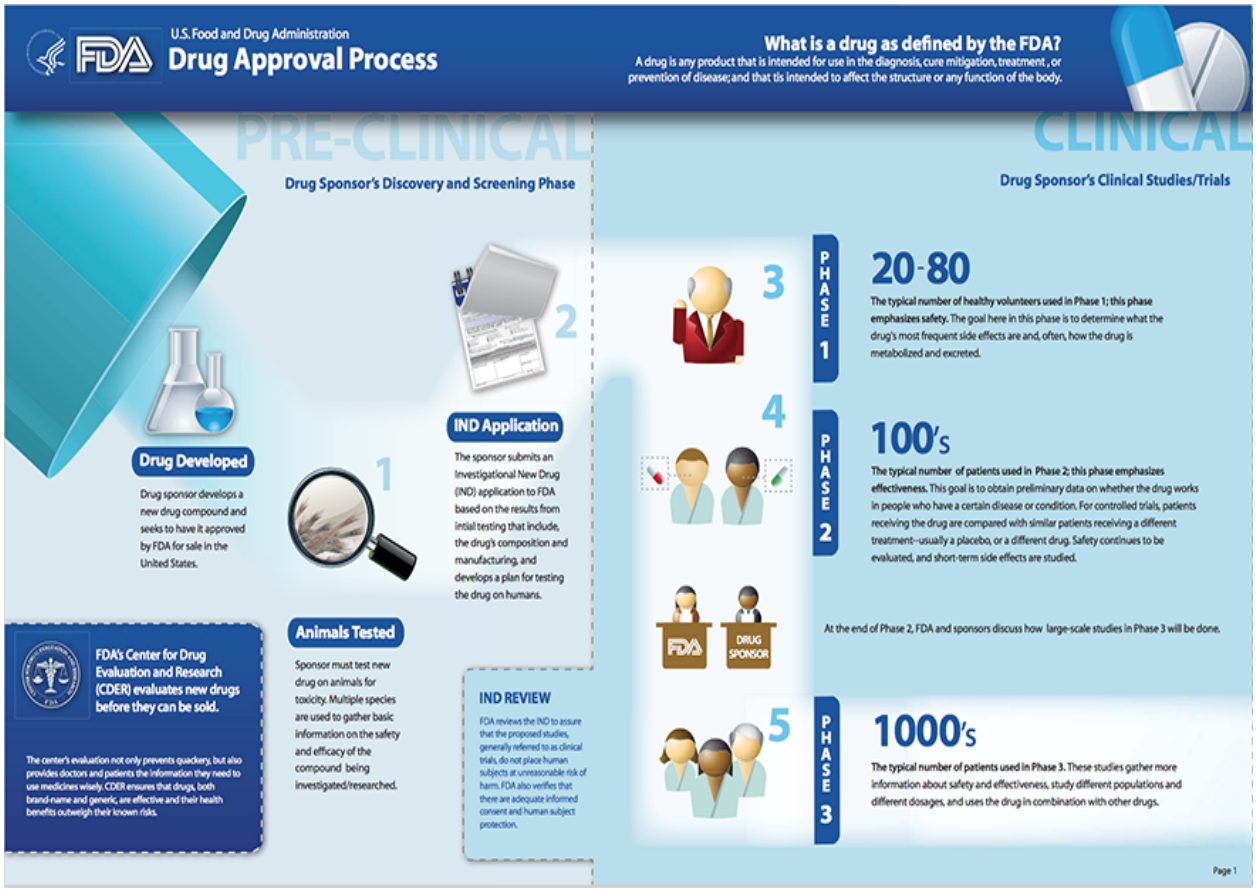


Figure 2. FDA Drug approval: Pre-clinical and clinical process (U.S. Food & Drug Administration, 2015b)

Figure 3. FDA Drug approval: NDA review and post-marketing (U.S. Food & Drug Administration, 2015b)

Cosmetic Regulations

Safety

In contrast, however, under the FD&C, regulation of cosmetic products (refer to Table 1) currently does not require FDA approval before they are marketed to consumers - with the caveat of establishing safety as the only critical factor evaluated (U.S. Food & Drug Administration, 2016). The FDA provides a list of its monitoring practices of cosmetic products with respect to safety per the following:

- Use of the Voluntary Cosmetic Registration Program (VCRP) which provides a database for cosmetic companies to report product formulations
- FDA inspections for proper manufacturing controls and practices, the periodic purchase and analysis of alerted products
- The Cosmetic Ingredient Review (CIR) expert panel used to assess safety of cosmetic ingredients based on published data (sources may include utilizing search engines PubMed and TOXNET)
- Reports from consumers and healthcare providers (U.S. Food & Drug Administration, 2016)

In addition to those supporting authorities addressed, the FDA collaborates with the Center for Food Safety and Applied Nutrition (CFSAN) which ensures cosmetic products are safe and properly labeled per the following regulating and governing responsibilities:

- Safety of cosmetic ingredients and finished products
- Activities dealing with proper labeling of cosmetics
- Research programs to address possible health risks associated with chemical or biological contaminants
- Post market and related compliance activities
- Industry and consumer education
- International standard and harmonization efforts (U.S. Food & Drug Administration, 2016)

Labeling

Currently, the two governing laws for cosmetic products, the FD&C Act and the Fair Packaging and Label Act (FPLA), both provide minimal enforcement with respect to legal action – with the FD&C merely prohibiting "the marketing of adulterated or misbranded cosmetics in interstate commerce" and the FPLA requiring cosmetic companies to list the ingredients within their product labels (Federal Trade Commission, 2013).

Under Sec. 301, the FD&C Act considers a product misbranded per the following (U.S. Food & Drug Administration, 2017a):

- Labeling is false or misleading
- Label does not state the following:
    - Name and address of the manufacturer, packer, or distributor
    - Net quantity of contents
- Required information is not stated prominently, with conspicuousness and in terms that it is read and understood by consumers under customary conditions of purchase and use
- Container or its fill is misleading

In addition, under Sec. 602, the FD&C Act provides a defined set of factors which categorizes a cosmetic product as "misleading" per the following (U.S. Food & Drug Administration, 2017a):

1. Representations made or suggested
2. Failure to reveal material facts:
    a. Material in light of such representations
    b. Material with respect to consequences resulting from the intended use

Under 15 U.S.C. 1451-1460, the FPLA governs that all packages and their respective labels provide consumers with accurate information with respect to quantity of contents and facilitate value comparisons (U.S. Food & Drug Administration, 2017a).

Ingredient List

In addition to safety and labeling governing laws, a standardized list of registered cosmetic ingredients is maintained under the International Nomenclature of Cosmetic Ingredients (INCI) system - which was established in the early 1970s by the Personal

Care Products Council (Personal Care Products Council, 2016). The INCI list is reviewed and assessed for safety through the Cosmetic Ingredient Review (CIR) committee (Cosmetic Ingredient Review, 2010a) which was established in 1976 and operates under a set of defined procedures (Cosmetic Ingredient Review, 2010b). The CIR, comprised of scientific, and medical government agencies - catalogues ingredients under four classifications:

1) Safe as currently used
2) Safe with qualifications
3) Unsafe
4) Insufficient information for a determination (Cosmetic Ingredient Review, 2010b)

With more companies investing in ways to amplify their traditional cosmetic skin care products, enter nanotech-based formulations.

The hybrid between nanotech and cosmetic products pose new questions of how to navigate and regulate this new industry with only a minimal percentage out of thousands of nano-enabled cosmetic products registered and assessment by the Cosmetic Industry Review panel and Consumer Products Inventory (CPI) for toxicity, properties, potential exposure pathways, and nanoparticle function (Project on Emerging Nanotechnologies, 2013). CPI is an online inventory of over 1600 nanotech-based consumer products that are marketed – a resource available for consumers, regulatory agencies, and manufacturers to obtain relevant data pertaining to nanoparticle function, properties, and toxicity (Project on Emerging Nanotechnologies, 2013).

Table 1. Regulatory Guidance Overview

Category	Primary Authority	Supporting Authority	Overview & Review Required
General	FDA	❑ National Institutes of Health (NIH) ❑ Environmental Protection Agency (EPA) ❑ United States Department of Agriculture (USDA) ❑ Federal Trade Commission (FTC) ❑ National Advertising Department of the Better Business Bureau (NAD) ❑ Consumer Product Safety Commission (CPSC)	To protect consumers from unsafe or deceptively labeled or packaged products by prohibiting the movement in interstate commerce of adulterated or misbranded food, drugs, devices, and cosmetics. Relevant Code/Law/Act: • 21 U.S.C. 321-392 • 21 CFR Part 1-2
Drug	FDA	❑ International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ❑ USP ❑ Center for Drug Evaluation and Research (CDER) ❑ Center for Food Safety and Applied Nutrition (CFSAN)	Statutory requirements for Premarket approval (PMA) Relevant Code/Law/Act: • Federal Food, Drug, and Cosmetic (FD&C) Act • Fair Packaging and Labeling (FP&L) Act
Cosmetic	FDA	❑ Center for Food Safety and Applied Nutrition (CFSAN) ❑ Personal Care Products Council (PCPC) ❑ Voluntary Cosmetic Registration Program (VCRP) ❑ Cosmetic Ingredient Review (CIR) ❑ International Nomenclature of Cosmetic Ingredients (INCI) system	No statutory requirements for PMA. Relevant Code/Law/Act: • Federal Food, Drug, and Cosmetic (FD&C) Act • Fair Packaging and Labeling (FP&L) Act • 21 CFR Part 700-701, 710, 720, 740
Nanotechnology	FDA	❑ National Nanotechnology Initiative (NNI) ❑ Nanotechnology Task Force ❑ Project on Emerging Nanotechnologies ❑ Nanotechnology Characterization Library	Relevant Code/Law/Act: • Federal Food, Drug, and Cosmetic (FD&C) Act • Fair Packaging and Labeling (FP&L) Act

General Claims

Although regulatory guidance seems to morph and adjust along with the current changing times and improved technologies; what still remains steadfast is establishing the product's intended use or claim. The intended use of a product may be established in various ways as indicated in the following:

- Claims stated on the product labeling, in advertising, on the Internet, or in other promotional materials. Certain claims may cause a product to be considered a drug, even if the product is marketed as if it were a cosmetic. Such claims establish the product as a drug because the intended use is to treat or prevent disease or otherwise affect the structure or functions of the human body.
- Consumer perception, which may be established through the product's reputation.

- Ingredients that cause a product to be considered a drug because they have a well-known (to the public and industry) therapeutic use (U.S. Food & Drug Administration, 2012)

An example of a product's intended use statement is with Silk Therapeutics® Purely Smooth moisturizer which claims to deliver the following: 1) fewer wrinkles and fine lines, 2) firmer skin, and 3) improved tone (texture and color) through the synergistic properties of their patented Silk Microcapsule™ Technology with rosehip oil, vitamin C and sodium anisate (Silk Therapeutics®, 2016). In the example with Silk Therapeutics®, each intended use claim does not seem to breach that of a therapeutic drug claim which would provide statements to cure, treat, or prevention a specific disease according to the FDA. However, codified interpretation still remains unclear.

Intended Use and Warning Letters

Unfortunately, the suggestion that a cosmetic product administers superior effects as compared to a competing brand/product based on intended use occurs far too often. Therefore, it is important to differentiate between two types of claims relative to intended use:

1) Claiming a cosmetic product imbibes certain improving properties based on ingredients and,
2) Claiming a cosmetic product provides therapeutic drug-like improvements.

Under the FD&C Act (sec. 201), a therapeutic drug claim would include statements of a product to be used "in the cure, mitigation, treatment, or prevention of disease" (U.S.

Food & Drug Administration, 2012). The avoidance of specific therapeutic statements allows cosmeceutical companies the advantage to market and sell products removed from strict federal regulations compared to drug company counterparts. However, established guidance which regulates how claims and intended use phrasing is still unclear. Therefore, it is with good reason why cosmeceutical companies continue to claim ambiguous therapeutic-like product claims. In fact, clarity in defining verbiage which classifies therapeutic use remains subjective to FDA inspectors across the board. So how do we expect companies to comply when clear guidance is still unestablished?

Issued warning letters can often provide some insight in determining what might be considered a violation to cosmetic claims posing as therapeutic drug claims. However, the FDA still has yet to provide meaningful guidance regarding specific word use and inference based on interchangeable phrasing.

Nanotechnology and Nanoparticles

As the goal to formulate and create cosmetic products with optimum skin absorbance and improved damage repair continues, nanotechnology is rapidly emerging as an ideal approach to deliver the active of choice transported through smaller drug-loading modalities with cosmetic formulations. So what really is nanotechnology? At its very definition, nanotechnology is the fabrication and production of materials with dimensions of at least 1 to 100 nanometers (nm) (Xia et al., 2003).

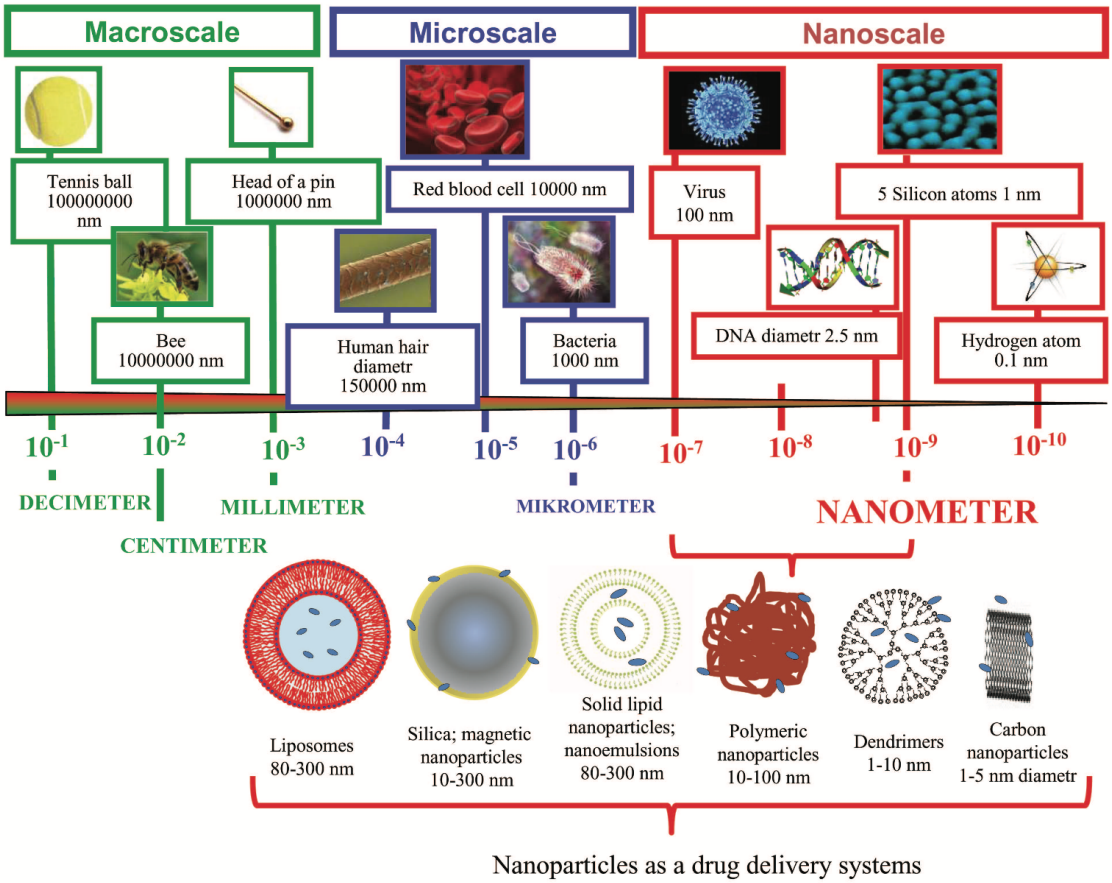


Figure 4. Nanoparticle drug delivery systems with relation to other scales (Wilczewska, Niemirowicz, Markiewicz, & Car, 2012)

Nanostructures are often touted as barely visible structures to the naked eye (refer to Figure 4) - offering impactful and highly discernible performances with a wide range of applications and profound use. The manifestation of nanostructures continues to infiltrate the cosmetic industry – with some common classifications under nanoliposomes, nanofibers, nanoemulsions, and even nanopigmentation (Ajazzuddin, Jeswani, & Jha, 2015). Traditionally speaking, nanoparticles are often categorized as either lipid-based or polymer-based (refer to Figure 5).

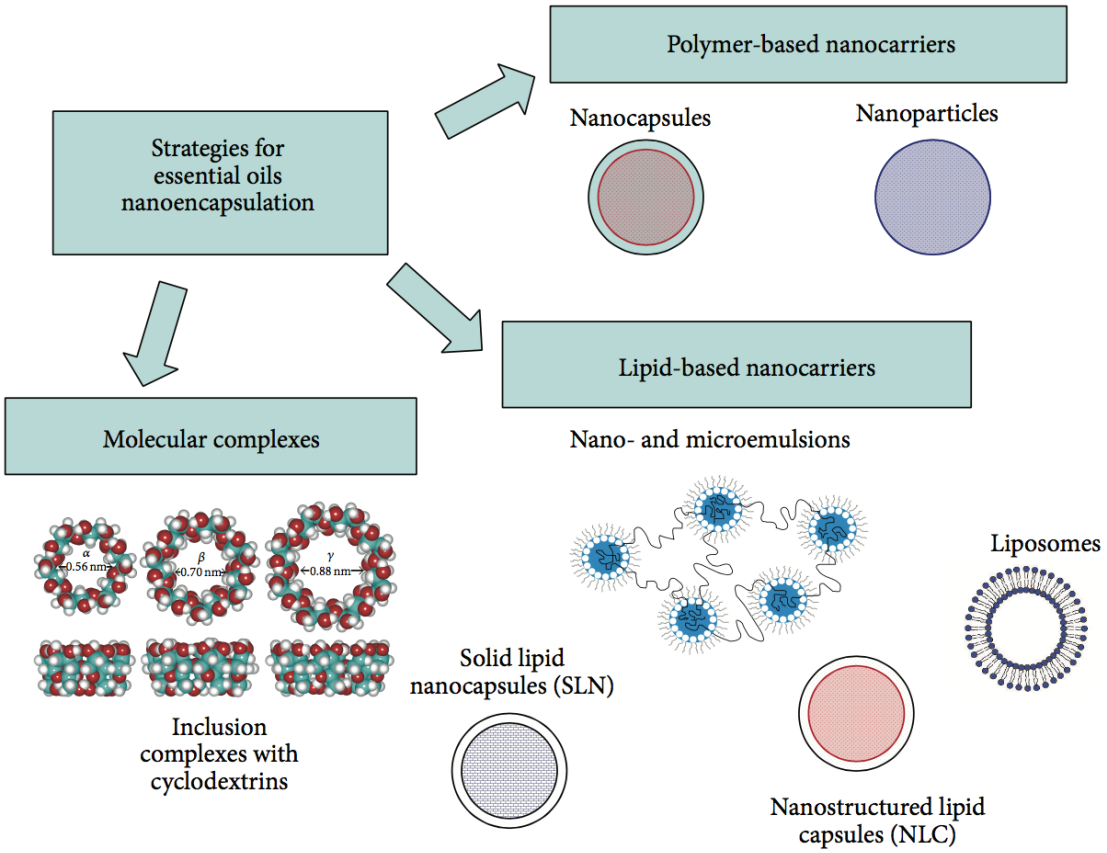


Figure 5. Nanoencapsulation strategies for essential oils (Bilia et al., 2014)

The use of nano-scaled engineered materials coupled with cosmetics functionalities have provided a range of amplified benefits, including increased transparency and solubility (Nohynek & Dufour, 2012) in addition to the possibility of quantifiable risks. With such intrinsic unknown risks posed, the concern of developing and deploying these revolutionary hyped structures with little regard to regulation can be unsettling. Gone are the days of traditional drug delivery systems, as new developments in engineering nanostructures employing varieties like liposomes (with its delivery benefits) encapsulating a drug active to fight diseases of all ailments (Cheema et al., 2007) - echo this research movement to look toward the future with the utilization of micro entities in

collaboration with biomaterials such as essential oils (for example rosehip oil). Therefore, the question still remains about the innate guidance of nanotechnology-based processes and whether there are potential risks being evaluated due to minimal or lenient regulation as compared to the stringent drug industry (Thayer, 2005).

One critical discussion is the potential health risks associated with nanotech-based products – such as its absorptive properties as it penetrates the human body through the epidermis (refer to Figure 6) and its unknown effects (Wilson, 2006).

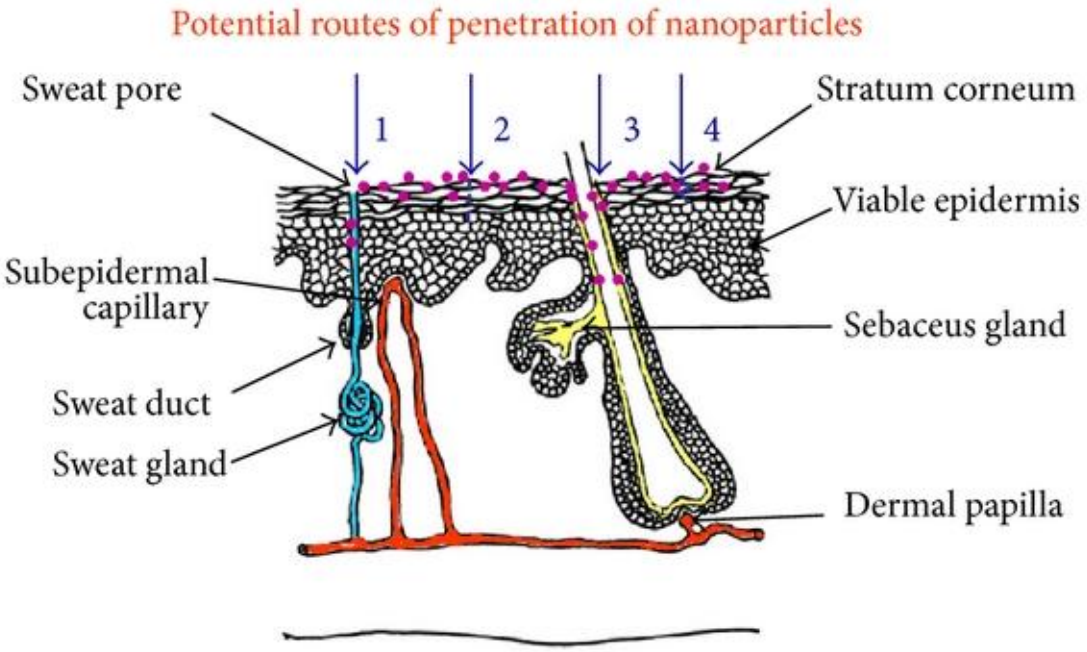


Figure 6. Skin nanoparticle drug delivery takes place in three major sites: stratum corneum surface through intracellular (2) and intercellular (4) penetration, furrows (1), and openings of hair follicles (3). The nanoparticles are shown in violet (Bilia et al., 2014)

However, a recent assessment (refer to Figure 7) detailed that the impact of nanomaterial on human health remained largely speculative compared its larger particles (Robichaud,

Tanzil, Weilenmann, & Wiesner, 2005). Therefore, the need to develop methods and systems that would provide impactful assessment of claims with respect to nano-based products is critical.

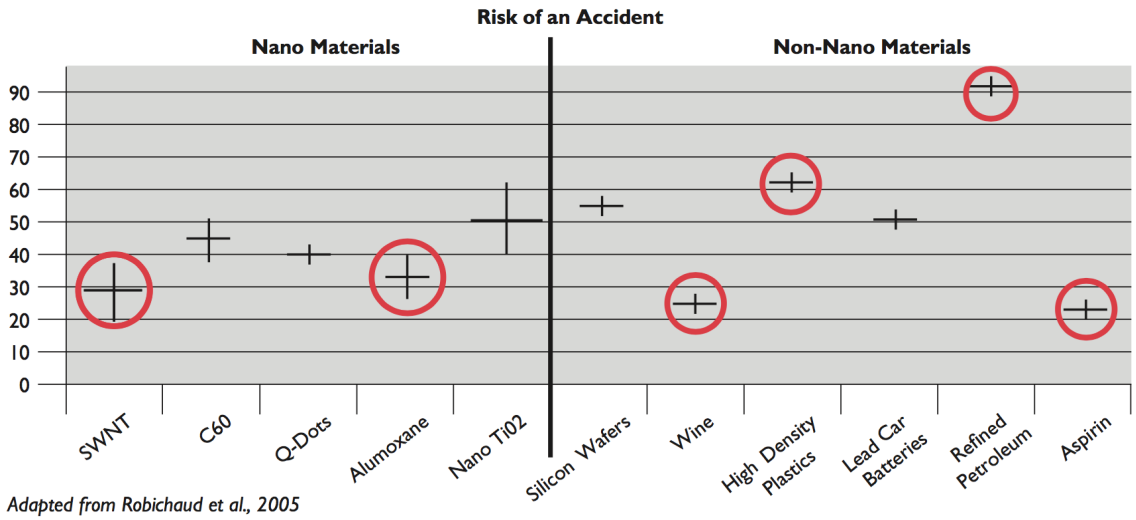


Figure 7. Risk assessment of Nano versus Non-nano materials (Robichaud et al., 2005)

Regulating Nanotechnology

In June 2014, the FDA released a document, which presented an overview of nonbinding recommendations to guide the industry with respect to safety of nanomaterials in cosmetic products (U.S. Food & Drug Administration, 2014b). Yet, the document itself is prefaced with the following statement – proof of the remaining uncertainty that prevails within the nano-cosmeceutical industry:

"This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss

an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance" (U.S. Food & Drug Administration, 2014b).

While regulation is relatively mild, various forums and organizations have been initiated in order to address the lack of consistency within the industry. Enter the FDA Nanotechnology Task Force, which recognizes a number of challenges associated with nanotech-derived products catalogued under its regulatory umbrella, including cosmetic containing nanoscale ingredients (U.S. Food & Drug Administration, 2007). Formed in August 2006, the task force addressed the following regulatory policy gaps and health effects relative to the nanotech communities. A press release in 2006 provided the preliminary framework for the initial elements of the task force and its obligations in which the organization would provide the following:

- Chair a public meeting to help the FDA further its understanding of developments in nanotechnology materials that pertain to FDA-regulated products, including new and emerging scientific issues such as those pertaining to biological interactions that may lead to either beneficial or adverse health effects.
- Assess the current state of scientific knowledge pertaining to nanotechnology materials for purposes of carrying out FDA's mission.
- Evaluate the effectiveness of the agency's regulatory approaches and authorities to meet any unique challenge that may be presented by the use of nanotechnology materials in FDA-regulated products.
- Explore opportunities to foster innovation using nanotechnology materials to develop safe and effective drugs, biologics and devices, and to develop safe foods, feeds, and cosmetics.
- Continue to strengthen FDA's collaborative relationships with other federal agencies, including the agencies participating in the National Nanotechnology Initiative (NNI) such as the National Institutes of Health (NIH), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA), as well as with foreign government regulatory bodies, international organizations, healthcare professionals, industry, consumers, and

other stakeholders to gather information regarding nanotechnology materials used or that could be used in FDA-regulated products.
- Consider appropriate vehicles for communicating with the public about the use of nanotechnology materials in FDA-regulated products.
- Submit its initial findings and recommendations to the Acting Commissioner within nine months of the public meeting (U.S. Food & Drug Administration, 2006)

At present, the task force has provided the initial framework and steps in order to determine effective regulatory guidance for the development of innovative and safe nanotech based products. However, within the task force, there still remained a lack of cohesiveness with respect to addressing the general regulatory factors that would guide the cosmeceutical industry. Therefore, in 2013, the Nanotechnology Task Force and the FDA (in collaboration with the National Nanotechnology Initiative, NNI) developed a regulatory science research plan with the goal to provide leadership which would address scientific gaps in knowledge, methods, and tools needed to make regulatory assessments relative to nano-based products (U.S. Food & Drug Administration, 2013a). The group assessed goals and needs of the following categories for nano-based products:

- Physico-chemical characterization
- Nonclinical models
- Risk assessment, risk communication, and risk characterization (U.S. Food & Drug Administration, 2013a).

Then, in June of 2014, the FDA provided the industry (manufacturers, suppliers, and importers) with nonbinding recommendations in evaluating products that involve the "application of Nanotechnology", "nanotechnology products" or involving materials "manufactured in the nanoscale range" (U.S. Food & Drug Administration, 2014a). The

document detailed the following points to be considered when looking to approve products manufactured after 2014:

1) "Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm)" (U.S. Food & Drug Administration, 2014a)
2) "Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm)" (U.S. Food & Drug Administration, 2014a)

From a clinical perspective; the Nanotechnology Task Force/FDA partnered with National Institute of Standards and Technology (NIST) and the National Cancer Institute's Nanotechnology Characterization Laboratory (NCL) to better understand biological interactions of nanoparticles through preclinical efficacy and toxicity studies (National Cancer Institute, 2016). Yet, there are still ongoing questions as to whether these organizations will or have become reliable resources, which validates the state of claims for the nanotech industry.

Silk Biomaterial

In more recent findings, scientists have determined that silkworm (*bombyx mori*) cocoons contain antioxidant properties – which has greatly fueled the increased interest in the study of harnessing this biomaterial for cosmetic purposes. This study evaluated its biomechanical properties and its enduring effect on both the research and cosmetic

communities. However, it is important to note the origins of the early discovery days, its commodity for trade, and its route to becoming today's scientifically studied material .

As such, we begin with the journey of the silk trade and its direct or indirect influence upon the medical field -- from the days of Louis Pasteur and bacterial infection to the early nineteenth century examining the biomaterial as suture potential. As scientists and physicians alike examined its biocompatibility properties, its benefits for controlled release as a drug delivery platform for a myriad of uses have become a popular topic of research. In fact, different silk components provide unique function as represented in Table 2.

Table 2. Function and Definition of Silk components (Nikitakis & Breslawec, 2014)

Component	Function	Definition
Fibroin	Bulking agent	Protein filament produced by the silkworm, *Bombyx mori* which together with Sericin composes Silk
Hydrolyzed Fibroin	Hair/Skin Conditioning	Hydrolysate of Fibroin derived by acid, enzyme or other with Sericin composes Silk. method of hydrolysis.
Hydrolyzed Sericin	Hair/Skin Conditioning	Hydrolysate of Sericin derived by acid, enzyme or other method of hydrolysis
Hydrolyzed Silk	Hair/Skin Conditioning	Hydrolysate of silk protein derived by acid, enzyme or other method of hydrolysis
Sericin	Hair/Skin Conditioning	Protein isolated from the silk produced by the silkworm, *Bombyx mori.*
Silk	Bulking agent	Fibrous protein obtained from cocoons of the silkworm.
Silk Extract	Skin Conditioning	Extract of silk fiber
Silk Powder	Bulking agent/ Skin Conditioning	Finely pulverized silk
Silkworm Cocoon Extract	Skin Conditioning/ Humectant	Extract of the cocoon of the silkworm, *Bombyx mori.*

Silk Biomaterial: Composition

Generally speaking, silk is a protein copolymer spun into fibers through Lepidoptera larvae or cocoons produced through spiders, scorpions, and silkworms (Altman et al., 2003). Most commonly available, silkworms (*bombyx mori*) produce cocoons made of protein-based silk fibroin (SF) core filaments and the surrounding antigenic gum-like protein silk sericin (SS) material (Altman et al., 2003) at 75% and 25% ± 5% of raw silk, respectively (Zhang et al., 2011). In addition, in 1988, silk in *Bombyx mori* was further evaluated and determined to contain other natural components and inorganic matter (refer to Table 3).

Table 3. Composition of silk in Bombyx mori (Gulrajani, 1988)

Component	%
Fibroin	70-80
Sericin	20-30
Wax matter	0.4-0.8
Carbohydrates	1.2-1.6
Inorganic matter	0.7
Pigment	0.2
Total	100

Silk fibroin is one of the strongest natural fibers – consisting of a heavy chain (Fib-H) at approximately 390 kilo Daltons (kDa) (refer to Figure 8a and Figure 8b) and a light chain (Fib-L) at approximately 26 kDa connected by a disulfide bond and glycoprotein named P25 (at 30 kDa) (Zhou et al., 2000). The heavy chain portion

contains a repetitive amino acid sequence of glycine (46%)-alanine (29%)-serine (12%) (Heslot, 1998), which self-assemble into strong hydrogen bond β-sheets in the presence of water (Altman et al., 2003). It is these stacked β-sheets (refer to Figure 9) that provide the protein-based material its robust mechanical property: insulation, water absorbency, and thermo tolerance (Mondal, Trivedy, & Nirmal Kumar, 2006).

a) **Total number of amino acids:** 5263
Molecular weight: 391,593 da

Amino acid	*# Residues*	*Mol %*
Ala (A)	1593	30.3%
Arg (R)	14	0.3%
Asn (N)	20	0.4%
Asp (D)	25	0.5%
Cys (C)	5	0.1%
Gln (Q)	10	0.2%
Glu (E)	30	0.6%
Gly (G)	2415	45.9%
His (H)	5	0.1%
Ile (I)	13	0.2%
Leu (L)	7	0.1%
Lys (K)	12	0.2%
Met (M)	4	0.1%
Phe (F)	29	0.6%
Pro (P)	14	0.3%
Ser (S)	635	12.1%
Thr (T)	47	0.9%
Trp (W)	11	0.2%
Tyr (Y)	277	5.3%
Val (V)	97	1.8%

b)

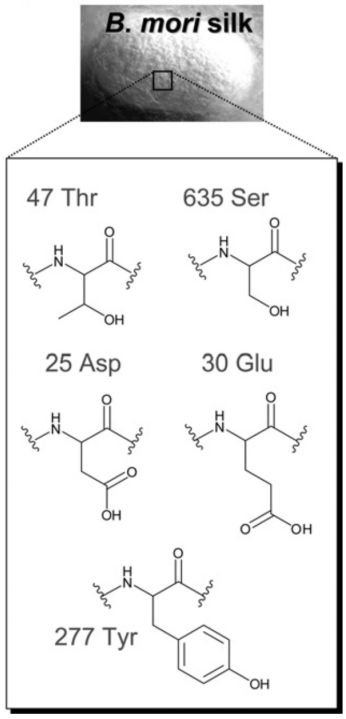


Figure 8. a) Amino acid composition of heavy chain of silk fibroin, b) Chemical structure of abundant amino acids in silk fibroin (Murphy & Kaplan, 2009).

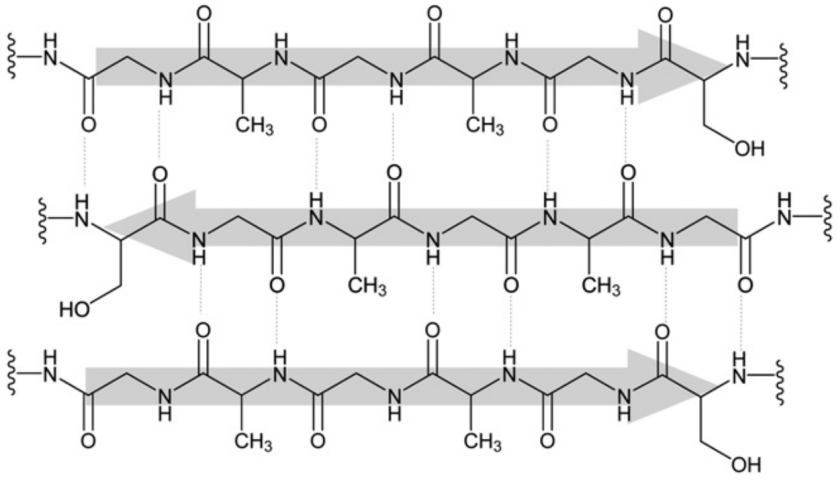


Figure 9. Silk fibroin β-sheet amino acid structure $(Gly\text{-}Ala\text{-}Gly\text{-}Ala\text{-}Gly\text{-}Ser)_6$ (Murphy & Kaplan, 2009)

Likewise, silk sericin contains an amino acid composition of serine (37%)-glycine (17%)- aspartate (16%) but is often selectively removed as a byproduct from fibroin during the silk manufacturing process (Heslot, 1998). Silk sericin protein has also been found to provide valuable attributes such as oxidation and UV resistance and chemo-protective properties (Mondal et al., 2006).

Silk Biomaterial: Biocompatibility

In addition to its fractionated components (refer to Table 3) offering protective and beneficial attributes; silk fibers, as a complete unit - provides potential biomedical uses with its demonstrative biocompatibility. A study conducted in 2003 evaluated the immune response activation by silk fibers with low-level inflammatory potential and no significant macrophage activation with sericin proteins (Panilaitis et al., 2003). However, the study observed significant tumor necrosis factors (TNF) released by fibroin particles but attributed the macrophage activation as a response to insoluble physical particulates (of varying size range and chemical composition) as opposed to a response mediated by actual silk (Panilaitis et al., 2003). Furthermore, a study conducted in 2005 determined that purified silk and implementation of improved fibroin isolation purification protocols resulted in minimal inflammatory responses – also suggesting biocompatibility (Meinel et al., 2005). Moreover, due to its overall physical and chemical elements, silk fibroin has been a widely researched candidate for drug delivery application (Liu, Zhang, Xu, &

Ouyang, 2009). In 2010, researchers evaluated silk protein spherical nanoparticles and explored its therapeutic potential as a drug delivery system through cellular uptake and control (Kundu, Chung, Kim, Tae, & Kundu, 2010). Imaging analysis and in vitro release assay results indicated silk fibroin protein were nontoxic – offering biocompatibility and good degradability as a potential carrier for drug delivery (Kundu et al., 2010). Finally, a vitamin E-loaded silk fibroin nanofibrous mat was evaluated for its possible use in skin care applications (Sheng et al., 2013). The results concluded that the vitamin E-loaded silk fibroin nanofibrous mats provided cell protection from oxidative stress induced by hydroperoxide – offering a novel potential for skin care product development (Sheng et al., 2013). The 2013 study was a complementary evaluation from a previous study, which concluded similar results using vitamin C-loaded silk fibroin nanofibrous mats (Fan et al., 2012).

Silk Biomaterial: Nanoparticle

Due to its previously discussed low immunogenicity and biocompatibility, development of silk-based nanoparticles for drug delivery purposes is gaining considerable attention and research momentum. Moreover, silk-based nanoparticle engineering entails mild laboratory preparation and offers considerable flexibility with respect to overall construction (in particle size and chemical concentration). Two identical silk nanoparticle methods were employed in separate research laboratories (refer

to Figure 10) (Rockwood et al., 2011) and (refer to Figure 11) (Wongpinyochit, Johnston, & Seib, 2016) due to its simplicity.

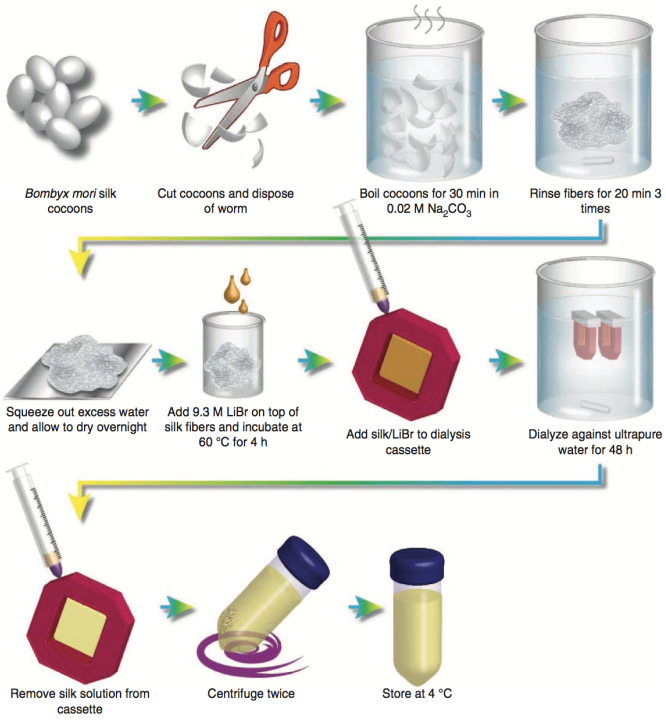


Figure 10. Silk fibroin extraction procedure (Rockwood et al., 2011)

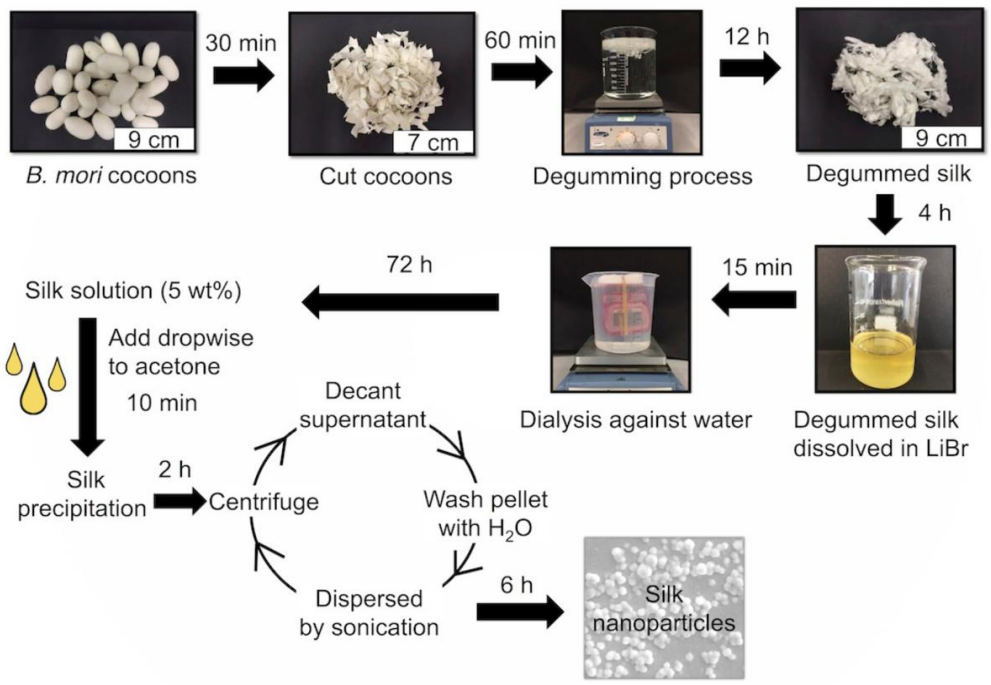


Figure 11. Reverse engineered silk solution and silk nanoparticles (Wongpinyochit et al., 2016)

Silk Biomaterial: Safety

Overall, based on a thorough assessment, the Cosmetic Ingredient Review (CIR) committee concluded that eight silk protein ingredients (this included fibroin and sericin) were safe for the use of cosmetics based on toxicity, depigmentation, cell proliferation, reproductive and developmental toxicity, irritation, phototoxicity, and immunological responses (CIR, 2016g). Now, the question still remains whether the CIR assessment may prove to be substantial with respect to regulation and as a validating metric.

Rosehip Oil

Scientific studies have shown that fruits of Rosa canina L. (known as rosehip) have been used for the treatment of various disorders, diseases, and medical ailments (Wenzig et al., 2008). Rosehip seed oil has been the subject of considerable clinical research and shown exceptional properties in reducing hyperpigmentation of scars (Valerón-Almazán, Gómez-Duaso, Santana-Molina, García-Bello, & Carretero, 2015). Among the more than 120 (and growing) rose species - *Rosa canina L*. (rosehip oil) is one of the most cultivated for its economic value in Turkey (refer to Figure 12).

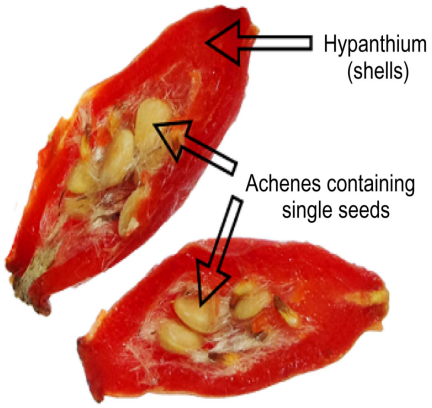


Figure 12. Botanical anatomy of a rosehip (shell and seed) (Winther, Campbell-Tofte, & Hansen, 2016)

Rosehip Oil: Composition

The overall chemical composition of *Rosa canina* can vary depending on various factors: cultivation practice, regional growth of the plant, maturity of the plant, phases of

biosynthesis of different *Rosa* species, and its overall storage. In fact, different rose components provide unique function as represented in Table 4.

Table 4. Function and Definition of Rose components (Nikitakis & Breslawec, 2014)

Component	Function	Definition
Rosa Canina Fruit Extract	Skin Conditioning	Extract of the fruit of Rosa canina. It is also defined as a hydroglycolic extract (water/butylene glycol) of 0.65% (maximum percentage) Rosa Canina Fruit Extract.
Rosa Canina Bud Extract	Skin Conditioning	Extract of the buds of Rosa canina.
Rosa Canina Flower	Fragrance	Is the petals of the flower of Rosa canina.
Rosa Canina Flower Extract	Astringent	Extract of the flowers of Rosa canina.
Rosa Canina Flower Oil	Skin Conditioning/ Fragrance	Volatile oil obtained from the flowers of Rosa canina.
Rosa Canina Flower Powder	Skin Conditioning/ Anti-acne	Powder obtained from the dried, ground flowers of Rosa canina.
Rosa Canina Fruit	Astringent	Fleshy fruit of Rosa canina.
Rosa Canina Fruit Juice	Astringent	Liquid expressed from the hips of Rosa canina.
Rosa Canina Leaf Extract	Skin Conditioning	Extract of the leaves of Rosa canina.
Rosa Canina Seed	Skin Conditioning	Seed of Rosa canina.
Rosa Canina Seed Extract	Skin Conditioning/ Humectant	Extract of the seeds of Rosa canina.
Rosa Canina Seed Powder	Exfoliants	Powder obtained from the dried, ground seeds of Rosa canina.

A study looking at differing chemical compositions of the *Rosa* species was conducted evaluating the following components: total phenolic amount, ascorbic acid, total soluble solids, total dry weight, total fat, fatty acids, pH, acidity, moisture, fruit color, and micro/macro elements (Ercisli, 2007). Ercisli concluded *Rosa canina* contained the highest total phenolic content of roughly 96 mg gallic acid equivalents

(GAE) per gram of dry weight (refer to Table 5), a total fat content of 1.78%, and possessed a dominant presence of fatty acid (refer to Table 6) with linoleic and α-linolenic acid (ALA) (refer to Figure 13) constituting a major portion (Ercisli, 2007). In addition to its total phenolic GAE profile, high concentrations of vitamin C (ascorbic acid) and flavonoids (refer to Table 7) have been examined in *Rosa canina* and other *Rosa* species (Nađpal et al., 2016).

Table 5. Total Phenolic Content of Rosa Species (Ercisli, 2007)

Species	Total phenolics (mg GAE/g DW)	Ascorbic acid (mg/100 ml)
Rosa canina	96	880
Rosa dumalis subsp. *boissieri*	84	943
Rosa dumalis subsp. *antalyensis*	85	864
Rosa villosa	73	727
Rosa pisiformis	79	811
Rosa pulverulenta	94	923

Table 6. Bioactive properties of Rosa canina (Winther et al., 2016)

Compound type	Compound name	Systematic nomenclature and lipid number*
Triterpene acid	Ursolic acid[18]	
	Oleanolic acid[18]	
	Betulinic acid[18]	
FAs	Lauric acid[19,20]	Dodecanoic acid (C 12:0)
	Myristic acid[20,21]	Tetradecanoid acid (C 14:0)
	Palmitic acid[19–21]	Hexadecanoic acid (C 16:0)
	Palmitoletic acid[20,21]	(C 16:1 ω-7)
	Stearic acid[20,21]	Octadecanoic acid (C 18:0)
	Oleic acid[20,21]	(C 18:1 ω-9)
	Linoleic acid[19–21]	*All-cis*-9,12-octadecadienoic acid (*cis*-C 18:2 ω-6)
	α-Linolenic acid[19,20]	*All-cis*-9,12,15-octadecatrienoic acid (*cis*-C 18:3 ω-3)
	Arachidic acid[19,20]	Eicosanoic acid (C 20:0)
	Behenic acid[20]	Docosanoic acid (C 22:0)
	Docosadienoic acid[19]	*All-cis*-13,16-docosadienoic acid (*cis*-C 22:2 ω-6)
Galactolipids	GOPO[5]	(2*S*)-1,2-di-*O*-[(9Z,12Z,15Z)-octadeca-9-12-15trienoyl]-3-*O*-*β*-D-galactopyranosyl glycerol

Table 7. Total phenolic, flavonoid and vitamin C content in R. canina and R. arvensis extracts (Nađpal et al., 2016)

Extracts	Content[a]		
	Total phenolics (mg GAE/g of dw)	Total flavonoid (mg QE/g of dw)	Vitamin C (mg/g of dw)
R. canina			
WF	74.6 ± 3.08 b	1.22 ± 0.02 f	1.96 ± 0.18 b
WD	61.0 ± 3.37 c	1.14 ± 0.04 fg	2.09 ± 0.20 b
MF	50.9 ± 3.60 c	0.65 ± 0.03 h	1.87 ± 0.14 b
MD	50.3 ± 2.26 c	0.63 ± 0.04 h	1.83 ± 0.17 b
P	96.2 ± 4.35 a	2.94 ± 0.02 b	3.73 ± 0.03 a
J	11.9 ± 0.84 ef	0.61 ± 0.03 h	0.56 ± 0.05 c
R. arvensis			
WF	6.63 ± 0.56 g	2.24 ± 0.05 c	0.13 ± 0.01 f
WD	9.75 ± 0.27 f	1.14 ± 0.02 g	0.23 ± 0.01 e
MF	13.8 ± 0.61 e	4.55 ± 0.10 a	0.32 ± 0.02 d
MD	18.7 ± 0.23 d	1.48 ± 0.01 e	0.42 ± 0.03 c
P	9.54 ± 0.67 f	1.76 ± 0.06 d	0.22 ± 0.02 e
J	7.40 ± 0.65 g	4.26 ± 0.05 a	0.14 ± 0.00 f

J – jam extract; MD – methanol extract of air-dried rose hips; MF – methanol extract of fresh rose hips; P – purée extract; WD – water extract of air-dried rose hips; WF – water extract of fresh rose hips.

[a] Values are means ± SD of three measurements. Means within each column with different letters (a–h) differ significantly ($p \leqslant 0.05$).

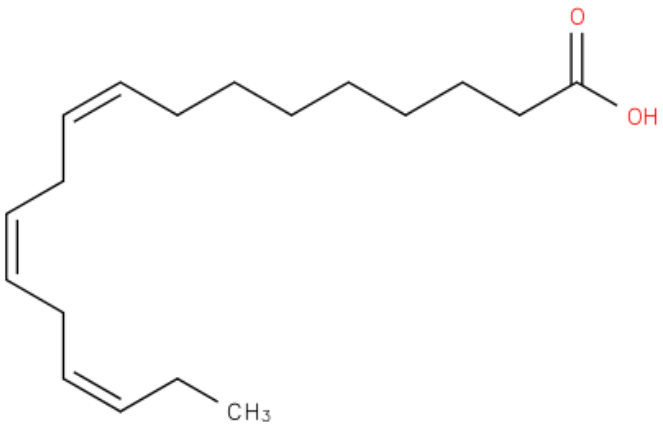


Figure 13. Alpha linolenic acid (ALA) (Pubchem, 2017)

Fatty acid (FA) composition of the rosehip seed was evaluated in 2014 and characterized to have approximately 35.9-54.8% of linoleic acid, 16.6-26.5% of α-linolenic acid, and 14.7-22.1% oleic acid (Ilyasoğlu, 2014; Ozcan, 2002; Szentmihályi, Vinkler, Lakatos, Illés, & Then, 2002; Zlatanov, 1999) in addition to galactolipid [GOPO;(2S)-1,2-di-O-[(9Z,12Z,15Z)-octadeca-9-12-15-trienoyl]-3-O-β-d-galactopyranosyl glycerol] (Larsen, Kharazmi, Christensen, & Christensen, 2003).

Rosehip Oil: Biocompatibility and Clinical Efficacy

A thorough review was conducted in 2008 to evaluate pharmacological efficacy and clinical effects of Rosa canina. The review found various literatures indicating high

antioxidant activity and anti-inflammatory results via analytical assays conducted utilizing FRAP, TEAC, and CAAP with indications that the phenolic portion provided as a contributing factor to its antioxidant properties (Chrubasik, Roufogalis, Müller-Ladner, & Chrubasik, 2008) and its anti-mutagenic/anti-carcinogenic effects (Kılıçgün & Altıner, 2010). Another review (C. Fan, Pacier, & Martirosyan, 2014) aimed at presenting the functional, medical, and physiological properties of rosehip determined that the abundance of ascorbic acid in *Rosa canina* (880mg/100mL) (Ercisli, 2007) and a bioactive compound identified as galactolipid (GOPO, refer to Figure 14) had also attributed to its biochemical antioxidant activity, anti-carcinogenic and anti-inflammatory effects (Larsen et al., 2003). Furthermore, various studies have demonstrated that rosehip and GOPO reduced inflammatory responses in differing *in vitro* cellular models (Schwager, Hoeller, Wolfram, & Richard, 2011) and that the *Rosa canina* extract contributed to immunomodulatory properties in vivo (Lattanzio et al., 2011).

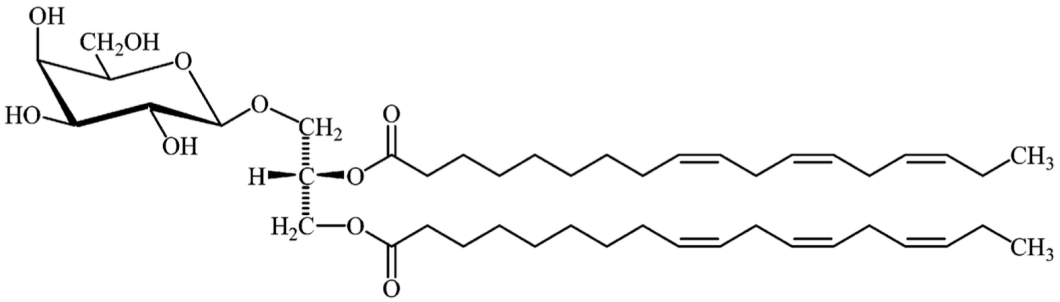


Figure 14. Chemical structure of the antiinflammatory galactolipid 1 isolated from rosehip (Larsen et al., 2003)

Although there is certainly a significant amount of information and research that has been performed on each component, attaining both authenticated and regulated data can be challenging. At present, there seems to be a lack of a validated and harmonized

assembly for policy makers, industry professionals, and general consumers to utilize with respect to ascertaining exact ingredient knowledge and the authenticity of product claims. Being able to navigate the barrage of research and studies performed with relevance to determining a product claim is still a challenging and cumbersome deficiency within the industry. Therefore, throughout this study we will examine all relevant research performed that is applicable to our determination of whether a product is correct in its established claim.

Evaluating Components and Testing

The restoring properties of essential oils such as rosehip seed oil (*rosa rubiginosa)* – extracted from seeds of the *rosa canina* shrub (Ilyasoğlu, 2014) – is rapidly becoming a staple within the intermixing backbone of skincare products. Moreover, application of essential oils in collaboration with nanotechnology was evaluated in a study published in 2016 which observed the stabilizing effects of nano-encapsulation of rosehip oil (RHO) and found that it decreased UVA and UVC oxidation of the oil itself (Contri et al., 2016).

It is also important to recognize that as generations become more cognizant of the beneficial properties present in plant and natural based materials – the growing awareness of consumers and its impact on biomaterial based drugs and cosmetics continue to increase. The growing phenomenon within the cosmetic industry and beauty industry is to tout claims of ingredients providing anti-aging effects grounded by antioxidant properties. Consumers continue to purchase expensive creams and serums that are

riddled with labeled hot terms such as “antioxidant fruit extract” or “anti-aging results using antioxidant ingredients from free radicals” – not necessarily having definable proof of what that necessarily entails. So we ask - what does that really mean? Are there validated assays or methods that can evaluate an ingredients antioxidant benefits or properties?

Viable Testing (In-house and Third Party)

As discussed earlier, with respect to aging factors, the deteriorative effects of environmental free radical exposure is a critical component when examining compounds with the potentiality to provide protection from said elements. The antioxidant values of biological samples listed are expressed in ORAC (Oxygen Radical Absorbance Capacity) units (Wayner, Burton, Ingold, & Locke, 1985) which is often used as a ranged scale to measure antioxidant capacity levels by the National Institute on Aging (NIA) at the National Institute of Health (NIH). Currently, one of the advantages of using the ORAC scale is to evaluate antioxidant capacities. The ORAC assay quantifies peroxyl radical absorbing capacity of antioxidants in serum or biological samples with the use of a fluorescent probe or indicator protein, β-phycoerthrin (β-PE) (Cao, Alessio, & Cutler, 1993). The loss of fluorescence of β-PE is an indication of the extent of damage from its reaction with the peroxyl radical. The protective effect of an antioxidant is measured by assessing the area under the fluorescence decay curve (AUC) of the sample as compared to that of the blank in which no antioxidant is present (Cao et al., 1993).

However, there is still considerable debate on the effectiveness and value that the ORAC scale provides. This study will provide evaluation as to whether the ORAC scale and developing methods may prove as a beneficial metric in validating cosmetic claims with respect to antioxidant and anti-aging properties.

Moreover, varying analytical assays have been developed to measure the antioxidant power or its capacity for resisting oxidative effects, which is often generated through environmental stresses and traditional signs of aging – these assays include the Ferric Reducing Ability of Plasma (FRAP) (Benzie and Strain 1996), Trolox equivalent antioxidant capacity (TEAC), and chemiluminescence analysis of antioxidant power (CAAP). These analytical assays may provide as a critical and reliable metric when determining truthful claims. Our study will evaluate whether companies utilize these similar analytical assays through internal testing or through the use of third party laboratories.

Outsourced Third Party Testing

Skin hydration is a component that can affect the aging process. Therefore, providing quantifiable proof whether skincare products used to promote continual skin hydration is effective and successful can be a resourceful tool. However, internally performed testing can often be criticized for their unbiased means of providing robust and neutral data.

As a result, third party or contract laboratories can often offer unbiased testing services as well as an additional array of assays. Outsourced companies, such as Bioalternatives (Bioalternatives, 2017) offer multiple validated (*in vitro* and *ex vivo*) assays and models that evaluate various aging effects based on ingredients used in cosmetic formulations which can measure the following:

- Skin aging
- Skin hydration and reinforcement of the skin barrier function
- Skin firmness and cohesion
- Skin protection and defense

Chapter II

Methods

The purpose of this study was to evaluate overall claims presented by companies (such as delivering optimum absorption while providing functional cosmetic benefits) with regards to two specific biomaterials (silk nanoparticles and rosehip oil). We analyzed said marketed claims through the following initial evaluation processing steps: 1) assessed overall claim(s) of the product/company, 2) provided a list of major ingredients that were relevant to product claim(s), 3) evaluated whether the company provides significant evidence to support their claims through:

- Clinical data, toxicology data, and case studies
- Patents
- Published scientific literature
- Company website verbiage confirming ingredient applicability
- Use of in-house or third party testing

When relevant, we looked at whether companies provide data to support antioxidant claims or performed claim specific testing using analytical methods. In addition, we utilized FDA recommended websites and organizations which provide material assessment such as the Cosmetic Ingredient Review (CIR).

We begin by providing the minimal assessments mandated by the FDA: safety and labeling. Under current law practices, a cosmetic product must be deemed safe for consumers when used according to directions on its established label.

Based on information/data gathered (or available), we utilized a categorical rating system and optimized the system to our current study. In addition, we employed the design of Stuart Pugh's selection matrix principles which is a systematic decision making process for the determination of a best concept, and is used in engineering to score new design concepts against a baseline design (Pugh, 1991).

Therefore, the following section details the methodology (refer to Figure 21) used throughout the study.

Curation of Products

As the focus of this study was to look at rosehip, silk, and rosehip-silk combination based products, we began by identifying specific cosmetic products that included key terminology (refer to Table 8). Then, through a Google and online beauty search, we began by selecting skincare products which had an anti-aging and skin moisturizing focus specifically for the face and body. These products ranged from serums, moisturizers, creams, lotions, powders, and oils. We coupled our internet search using online beauty stores (refer to Table 8) applying the same ingredient specific terminology search.

Table 8. Terminology/Ingredient Key and Beauty

Rosehip	Silk	Online Search
• rosehip • rosehip oil • rosehip seed • rosehip seed oil • rosa canina • rosa rubiginosa • rosa damascena • rosa mosqueta	• silk • silk sericin • silk fibroin • hydrolyzed silk • silk (serica) powder • silk proteins • silk amino acid • silk extract	Google ("Google," 2017a) Sephora ("Sephora," 2017) Ulta Beauty ("Ulta Beauty," 2017) Dermstore ("Dermstore," 2017) Skinstore ("SkinStore," 2017) Beautylish ("Beautylish," 2017) Bluemercury ("Bluemercury," 2017) The Detox Market ("The Detox Market," 2017)

Selection of Products

Although the acquired list of rosehip and silk based products was extensive, we limited our product selection to focus primarily within the United States (U.S.) and U.S cosmetics. Therefore, all products selected in our assessment were manufactured through U.S. based companies. As a result, we established our focus on the current regulatory landscape applied within the U.S industry and its market.

We continued to categorize these products based on four (4) critical categories:

- Type of ingredient focus
  - Rosehip or rose based
  - Silk
  - Rose + silk nanotechnology combo
- The product would include a maximum of thirty (30) ingredients (excluding: water, fragrances, preservatives, and color ingredients).
- Product must be readily available to consumers
- Size of the company that manufactured the product (large, medium, small).

In order to minimize redundant conclusions for similar products, we selected a maximum of two (2) companies from each size for each ingredient focus. The intent of

selecting different company employee sizes was to capture a variety and range of availability to labor and resources relative to effective product claim substantiation.

We based the size of each company according to definitions established in an employment and payroll summary published in 2012. The established sizes were as follows (Caruso, 2015)

- Large (500 or more employees)
- Medium (100 to 499 employees)
- Small (99 to fewer than 20 employees)

We determined relative employee size for each company through a Buzzfile search. The Buzzfile ("Buzzfile," 2017) website presents a comprehensive company database which provides detailed public access of companies within the U.S. The extracted employee number was cross-referenced with a LinkedIn ("LinkedIn," 2017) employee count search for each company to establish the categorical company size.

Although the cosmetic and beauty industry contains a vast array of products, we recognize the possibility that available or identified products specific to our selection criterion may not be achievable within the confines of company size and the material of interest.

Communication

Once our list of products were identified, we contacted each company (refer to Figure 15) through two relevant portals: company email and corporate online form.

In either email or corporate form sent (refer to Figure 15), we requested information regarding whether the company would be able to provide data or documentation to support their product claims with the following:

- Clinical data [ClinicalTrials.gov (National Institutes of Health, 2017b)] or case studies
- Patents (United States Patent and Trademark Office, 1994)
- Published scientific literature
    - NIH (National Institutes of Health, 2017a)
    - PubMed (National Center for Biotechnology Information, 2017)
    - Toxicology Data Network (TOXNET) (National Institute of Health, 2017)
    - Company website verbiage confirming ingredient applicability.
- Product testing (in-house or third party)

Dear (insert Company Name),

I was searching on your website to find any information regarding clinical or research data to support your product claims. Would you be able to direct me to that information or direct me to the correct personnel within your company that can provide that information?

More specifically, I would be interested in (insert Company Product) or any other of your (insert biomaterial focus) containing products. Any help would be greatly appreciated!

I'm currently working on curating research data with respect to (insert biomaterial focus) products through my Masters project at Harvard University. Any information that you can provide would be included as a contributor with respect to the populated data. My research is looking at how the beauty industry supports its product claims through research (if any).

So any information outside of the general statements (from your website) that it provides certain aesthetic changes or improvements to the skin would be helpful. More specifically whether you review the following:

- Clinical data or case studies
- Patents
- Published scientific literature
- Provide product analytical testing (in-house or third party)

The more assistance you can provide with regards to transparency of your product and any studies conducted -- would be greatly appreciated. Again, I would be including your company in a list of research collaborators if given permission.

I look forward to hearing from you.

Best,
Emily Sudhyadhom

Figure 15. Sample Email/Corporate Form Verbiage.

We allotted for at least a two to three month margin of communication time - in order for applicable representatives of each company to respond. As access to regulatory

documentation and scientific data can often be limited to ordinary consumers, the communication (via email or online corporate form) portal is among the most readily available tool to determine claim substantiation from each company. Therefore, company response (or lack thereof) and transparency was factored into our overall claims substantiation assessment with allowance for legal and proprietary sensitivities.

Collection of Ingredients and Claims

Upon reaching out to each individual company, we began to collect full ingredient lists and applicable product claims for each assessed product. Ingredient list and stated claims were collected through company website portals and labeled packaging.

Establishing Safety

To confirm the FDA's critical criteria of safety, we reviewed all labeled ingredients listed and used the following recommended programs and organizations (U.S. Food & Drug Administration, 2016):

- Voluntary Cosmetic Registration Program (VCRP).
- Cosmetic Ingredient Review (CIR)
- Reports from consumers and healthcare providers

We reviewed all current CIR ingredient assessments for safety under four classifications:

1) Safe as currently used
2) Safe with qualifications
3) Unsafe

4) Insufficient information for a determination (Cosmetic Ingredient Review, 2010b)

In addition, we utilized the Skin Deep® Cosmetic Database ("Skin Deep® Cosmetics Database," 2017a) scoring system to provide additional assessment of individual ingredient safety. Assessment and review of all ingredients established within the Skin Deep® Cosmetic Database is performed by staff scientists as part of the Environmental Working Group (EWG) ("EWG," 2015), a third party organization. The purpose behind the Skin Deep® Cosmetic Database is to review the safety of products and its individual ingredients - which is not currently performed by the the FDA or any regulatory agencies prior to being sold. EWG's Skin Deep® Cosmetic Database utilizes data extracted from primary/secondary references and warnings which are based on available toxicity and regulatory studies. Rigorous safety and hazardous assessment relative to ingredients, products, and companies are given a hazard score of 1-10 and data score ranging from None to Robust (refer to Figure 16) ("Skin Deep® Cosmetics Database," 2017b).

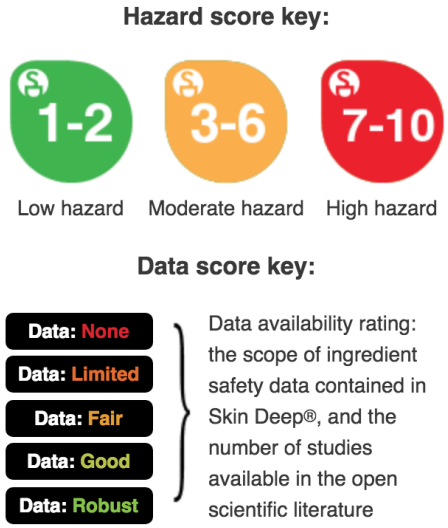


Figure 16. EWG's Skin Deep® Cosmetic Database Hazard Score Key ("Skin Deep® Cosmetics Database," 2017b)

Currently, the EWG has identified nine ingredients which are considered non-harmful as these ingredients have been assigned a hazard score of 1 with robust data availability - these ingredients include: Aare Avena Sativa (Oat) Kernel Meal, Blue Green Algae, Cellulose, Colloidal Oatmeal, Honey, Sea Salt, Sodium Chloride, Sucrose, and Water ("Skin Deep® Cosmetics Database," 2017b).

Using the Skin Deep® Cosmetic Database, we searched each product (as a whole) to determine whether it was automatically given a EWG Hazard and data score. If the product (as a whole) was not pre-identified by EWG within the database, we manually populated each EWG score reports per EWG's Build Your Own Report (EWG, 2017) option for each unavailable product - by providing the required information.

Verifying Cosmetic Labeling

In addition to establishing overall safety, the FDA requires that all products comply with two basic governing labeling acts (refer to Table 9):

- Federal Food, Drug, and Cosmetic (FD&C) Act
- Fair Packaging and Labeling (FP&L) Act.

Table 9. Cosmetic Labeling Laws (U.S. Food & Drug Administration, 2017a)

Laws	Defined As	Guidelines
Sec. 301, FD&C Act	Cosmetic is considered misbranded if:	Labeling is misleading or false Contents or quantity of the container is misleading Label does not provide the following: Name and address of the manufacturer/distributor Net quantity of the contents of the container.
Sec. 602, FD&C Act	Cosmetic is considered "misleading" if:	Representations made or suggested Failure to reveal material facts: Material in light of such representations Material with respect to consequences resulting from the intended use

We reviewed product packaging and labeled ingredients listed per FD&C Sec 301 and 602 - to determine whether each product met minimal proper labeling guidelines (U.S. Food & Drug Administration, 2017a).

Exclusion of Irrelevant Ingredients

In order to thoroughly examine and collect relevant data, we eliminated ingredients that were deemed safe (based upon regulatory assessments and database) and categorized under the following function:

- Solvents
- Fragrances/Parfum (refer to Table 10)
- Emulsifying/Stabilizing/Binding/Viscosity Agent
- Bulking Agent
- Surfactants/Solubilizing Agent
- Buffering Agent
- Preservatives
- Color Additives or Colorants (refer to Table 10)

Table 10. Additional Safety Review

Function	Description	Reference
Fragrances/Parfum	Safety determined by the Research Institute for Fragrance Materials (RIFM).	Part D (Cosmetic Ingredient Review, 2010b)
Color Additives or Colorants	Safety determined under 21 C.F.R. Part 71.	Part D (Cosmetic Ingredient Review, 2010b)

These ingredients were eliminated unless explicitly identified as a vital ingredient by the manufacturer with respect to its product claim. Once primary ingredients to the total formulation were established, we reviewed each of components through evaluating available academic publications, clinical studies, patents, warning letters, and third party certifications.

Collecting Data

Research and Clinical Data

Applicable and supportive research is a key factor when substantiating claim relevance. Whether it was through product-specific driven research or ingredient-specific studies; we began by identifying an extensive catalogue of publications that included key terminology similar to Table 8, product specific names, product specific ingredients, and at least four (4) additional relevant claim descriptors per the following examples:

- Aging
- Antioxidant
- Composition
- Hydrating
- Moisture
- Skin
- Cosmetic
- Nanotechnology

We utilized online search engines (such as PubMed, NIH, Toxnet, ClinicalTrials) and CIR assessment in order to populate key research relevant to the following:

- Product of interest
- Each ingredient listed.

We reviewed the total populated search results versus applicable product/ingredient-specific research to overall claim substantiation in our assessment (refer to Table 11).

Table 11. Sample Data Search

Primary Search Term	Relevant Claim Descriptor Search Term	Relevant Total Search Results
"*rosa canina*"	"*aging*"	
"*silk*"	"hydrating"	
"*product name*"		

Patents

In addition, we performed an identical keyword (refer to Table 8) and product specific search with respect to patents through the United States Patent and Trademark Office (USPTO) (United States Patent and Trademark Office, 2009), Google Patents Public Datasets (Google, 2017b), and World Intellectual Property Organization (WIPO) (WIPO, 2017).

We reviewed total populated product-specific search results versus applicable product-specific patents to overall claim substantiation in our total (refer to Table 12).

Due to the candid description of information revealed within patents; if a company filed for product specific patents, we recognized this transparency and applied a positive scoring toward claim substantiation.

Table 12. Sample Patent Search

Key Search Term	Total Search Results	Applicable Patents
"*rosa canina*"		
"*silk*"		
"*product name*"		

Manufacturer Response

After our initial contact and allotted timeframe transpired, we finalized all relevant communication with identified companies and grouped whether the company/manufacturer responded with the following:

- Provided supportive documentation
- Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations.
- Declined to provide documentation to support claim.
- No communication response

Product Testing (In-house and Third Party)

In addition to review of the manufacturer's response, we evaluated whether the company website, available published literature, or clinical references - offered an insight to level of testing (internal or through third party laboratories). Again, we grouped whether the company responded with the following:

- Confirmed testing and provided supportive documentation
- Confirmed testing but declined to provide supportive data due to proprietary and commercially sensitive limitations.

- Declined to provide documentation to verify testing.
- No communication response

If the company confirmed testing, we requested whether the company would elaborate into the type of testing. More specifically, we looked to determine whether companies performed advanced analytical testing with respect to product claim, clinical studies, or basic testing under the following:

- Visual/Observation
- Application
- Smell

If the company confirmed to using analytical advanced testing with respect to product claims, we inquired insight upon their established methods based on our initial research list of suggested assays per the following:

- ORAC (Oxygen Radical Absorbance Capacity)
- Ferric Reducing Ability of Plasma (FRAP)
- Trolox equivalent antioxidant capacity (TEAC)
- Chemiluminescence analysis of antioxidant power (CAAP)

If the company did not perform internal testing, we inquired insight to whether utilization of contract research organizations or third-party labs (such as Bioalternatives) was employed. Third party laboratories, like Bioalternatives (Bioalternatives, 2016a), often provide a range of validated methods and models that tests for products in preclinical development to active ingredients in cosmetic formulations.

In fact, in 2016, Bioalternatives published a study regarding their use of a developed simple skin model which mimicked the aged epidermis compared to a normal (or young) dermis layer. The advantage of this *in vitro* model would give companies

developing cosmetic skincare products a tool with the features of an aged skin epidermis - allowing for evaluation of effects of ingredients in their cosmetic formulation. This model would provide as a control compared to the variability of human volunteers or skin samples used *ex vivo* (Bioalternatives, 2016b).

Decision Making

Pugh's Matrix

Upon completion of our data collection, we employed the concept behind Pugh's methodology in order to provide as an aid in the evaluation process looking at multiple criteria converged into one definitive and quantifiable solution (Pugh, 1991). As this study involved multivariate analysis of relevant publications, patents, clinical data, testing, and third party certification - it was critical to synchronize the combined assessment and provide a standardized approach at determining robust claim substantiation. The concept behind the Pugh's decision making process often takes the form of (refer to Table 13) a matrix which utilizes applicable criteria that is critical in order to standardize priority with respect to selection and determination. In other words, products are individually rated relative to a selected baseline with the following score:

- Positive (+) for better or abundant
- Negative (-) for deficient or worse
- Zero (0) for neutral or same.

This approach provided as an unbiased and quantifiable look at determining claim substantiation assessment and enabled simultaneous evaluation of multiple requirements.

Table 13. Basic Pugh's Matrix Design

Criteria	Weight	Product X (Baseline)	Product 1	Product 2	Product 3
Criteria 1	10	0	+	-	0
Criteria 2	7	0	-	0	+
Criteria 3	5	0	0	+	-
Criteria 4	3	0	+	-	0
Sum of (+)'s		0	2	1	1
Sum of (-)'s		0	1	2	1
Sum of (0)'s		4	1	1	2
Weighted (+)'s		0	13	5	7
Weighted (-)'s		0	7	13	5
Score: Weighted (+)'s - Weighted (-)'s		0	6	8	2

For the purposes of our evaluation, we utilized the concept behind the Pugh's approach and modified our matrix based on evaluation criterions using weighted values of a range from one to ten (1-10) - with 10 representing at a high criticality weight and 1 representing at a low criticality weight. Moreover, our goal was to look at the overall framework (data, regulatory bodies, third party organizations) with the current cosmeceutical industry and provide a complete assessment to establishing whether claims were being properly substantiated.

Baseline Product

As the need for a baseline product is certainly warranted in order to evaluate our selected products, we opted to establish a defined Product X. If claim substantiation were driven by a standardized list of absolutes which were mandated by governing bodies, Product X would likely include the following ideal minimum requirements (refer to Table 14):

Table 14. Baseline Product X

Product X
Be safe Meet minimum labeling requirements (FD&C Act; Sec 301 & 602) Provide reasonable claim Include full ingredient list on packaging Provide at least one research publication (per product specific or for each ingredient listed) that supports product claim. Provide at least one relevant clinical study (per product specific or for each ingredient listed) that supports product claim. Confirms claim specific testing (in-house or third party) Manufacturer provide full communication and transparency to academic/industry/beauty professionals and consumers

This list (refer to Table 14) of minimum requirements was used as our baseline in order to evaluate our selected list of products.

Additional Components (Positive and Negative)

In addition, factors such as available third party certification, regulatory warning letters, and unidentified ingredients were included within the matrix to provide as an additional component with respect to claim substantiation.

Third party certification can often provide significant support in confirming specific claim aspects. We reviewed whether each company was verified with Third Party Certification for the following:

- Safety
    - EWG Verified/Skin Deep® Database ("Skin Deep® Cosmetics Database," 2017a)
    - Think Dirty® (Think Dirty, 2015)

We utilized the Think Dirty® app, a mobile application founded in 2012 which provides consumers with a "on the go" tool in understanding ingredients with respect to their personal care products. Think Dirty focused exclusively on the chemical content of each product in question and utilized a rating system based on documented risk of carcinogenicity, developmental/reproductive toxicity, allergenicity, and immunotoxicity (Think Dirty, 2015).

Moreover, the Think Dirty® app performs its evaluation in collaboration with an advisory board within relevant fields such as medical, environmental, safety, and toxicology areas. In addition, Think Dirty® works closely with the "FDA, Health Canada, European Medicines Agency, Environment Canada, the US Environmental Protection Agency and other related government and not-for-profit agencies" and "rigorous third party certifiers" (Think Dirty, 2012).

As regulatory warning letters are considered as an undesirable criteria, we reversed the scoring of the (+)'s and (-)'s to accurately include the supplementary component in the matrix. In other words, a higher amount of regulatory warning letters as compared to the baseline product would receive a negative (-) score and lower amount

of regulatory warning letters provided as compared to the baseline product would receive a positive (+) score. In addition, any product specific warning letters uncovered were given a higher weighted score relative to a general company warning letter.

Finally, unidentified or irrelevant ingredients examined that do not have significant bearing on overall product performance based on substantiated claim will also be included within the decision making matrix (refer to). In other words, a higher amount of unidentified or irrelevant ingredients as compared to the baseline product would receive a negative (-) score and a lower amount of unidentified or irrelevant ingredients as compared to the baseline product would receive a positive (+) score.

Evaluation Criterions

Next, we began by formatting our decision making matrix with the left column comprised with the evaluation criterions used (refer to Figure 17). The criterions are represented as broad concepts that were evaluated per the following:

- Safety & Labeling (refer to Table 29)
- Examining Products (refer to Table 30)

References (refer to

- Table 31)
- Clinical (refer to Table 32)
- Product Testing (refer to Table 33)
- Manufacturer Response (refer to Table 34)

- Patents (refer to Table 35)
- Additional (Positives) (refer to Table 36)
    - Third Party Certification
- Additional (Negatives) (refer to Table 37)
    - Regulatory warning Letters
    - Unidentified Ingredients

			Product Number					
Criteria	**Description**	**Weight (1-10)**	**Baseline (Product X)**	**High Claim Substantiated Sample Product**	**Low Claim Substantiated Sample Product**	**1**	**2**	**3**
Safety & Labeling	Safety	10	0	+	-			
	Labeling	10	0	+	-			
Examining Products	Claims	1	0	+	-			
	Ingredients	10	0	+	-			
References	Product Specific	2	0	+	-			
	Ingredient Specific	5	0	+	-			
Clinical	Product Specific	3	0	+	-			
	Ingredient Specific	3	0	+	-			
Product Testing	Manufacturer Information	5	0	+	-			
Manufacturer Response	Manufacturer Information	3	0	+	-			
Patents	Product Specific	4	0	+	-			
	Ingredient Specific	1	0	+	-			
Additional (Positive)	Third Party Certification	1	0	+	-			
Additional (Negative)	Warning Letters (General Company)	10	0	-	+			
	Warning Letters (Product Specific)	10	0	-	+			
	Unidentified Ingredients	2	0	+	-			
	Sum of (+)'s		0	14	2	0	0	0
	Sum of (-)'s		0	2	14	0	0	0
	Sum of (0)'s		16	0	0	0	0	0
	Weighted Sum Positives		0	60	20	0	0	0
	Weighted Sum Negatives		0	20	60	0	0	0
	Score: Weighted Positives - Weighted Negatives		0	40	-40	0	0	0

Figure 17. Modified Pugh's matrix

Vance Metric

In an effort to substantiate claims related to each product, we then created a metric table similar to a study in 2015 (refer to Table 15) - based on information/data gathered (or available). The table provided a categorical rating system of 1-5 (Vance et al., 2015). We optimized the table in collaboration with our Pugh's matrix for our current

study. In other words, our optimized design utilizes the 1-5 rating system in collaboration with Stuart Pugh's methodology (Pugh, 1991).

Table 15. Claims Metric Table (Vance et al., 2015)

Category	Description	Manufacturer Claims to Use Nanotechnology	Manufacturer Provides Supporting Information	Third-Party Information is Available	Compelling Information From Multiple Sources Is Available
1	Extensively Verified Claim				
2	Verified Claim				
3	Manufacturer-Supported Claim				
4	Unsupported Claim				
5	Not Advertised by Manufacturer				

We found that our scoring system evaluated each product with a total score of -40 to 40, with unsupported to high claim substantiation, respectively. We ranked scores according to the following (refer to Table 16):

Table 16. Final Claim Substantiation Ranking

Pugh's Score	Category	Description
30-40	1	Extensively High Claim Substantiation
19-29	2	High Claim Substantiation
8-18	3	Medium Claim Substantiation
1-7	4	Low Claim Substantiation
-40-0	5	Unsupported Claim Substantiation

Chapter III

Results

Nothing is more confusing than trying to establish and understand product claims regulations. It is hard to believe that at present, the current regulatory landscape still lacks essential harmonization with comparison to its drug counterpart. Consumers often find themselves plagued with question such as:

- Is my product or ingredient safe?
- Who is the primary regulating body that governs this product?
- What evidence is used for company stated claims relative to my product?
- How do I know that I'm being protected as a consumer?

These are but a few questions that plague the needs and desires of consumers these days. With a quick cursory review of how to retrieve information; it is often daunting to try to navigate the complicated landscape of regulations, marketing, and claims. And as the beauty market continues to expand its reach into science-based claims with ingredients that suggests therapeutic effects, the cosmeceutical industry is quickly becoming a lucrative market with little or lack of regulating conformity.

If claims are being stated; how is the industry providing clinical, statistical, and validated data which supports these assertions? Our conducted study reviewed hundreds of peer-reviewed publications, clinical studies, and various other criteria; in order to ascertain and confirm claim relevance.

The results extracted in this study were collected from February 01, 2017 through October 31, 2017.

Collected Product List, Ingredients, and Claims

Our key terminology (refer to Table 8) search resulted in thirteen (13) identified products (refer to Table 38) under the following established criteria:

- Type of ingredient focus
    1) Rosehip or rose based
    2) Silk
    3) Rose + silk nanotechnology combo
- Maximum of thirty (30) ingredients
- Product must be readily available to consumers
- Company Size (large, medium, small)
- United States-based companies

Our list of ingredients (refer to Table 39) and product claims (refer to Table 40 and Table 41) were obtained from both packaging and manufacturer website.

Manufacturer Communication and Transparency

Understanding claims aside, how does a consumer validate or verify that certain products actually provide the promise that is advertised? At present, the primary mode of access for consumers is establishing and inquiring information directly from the company/manufacturer of interest regarding added data or information relative to product claims. Therefore, the importance of the company transparency and providing a response to the nature of consumer queries remains critical.

As such, we contacted all companies listed in Table 38 and allotted for the minimum two to three month margin of communication time in order for applicable company representatives to respond. We tabulated our findings based on the following manufacturer/company response (refer to Table 17):

- Provided supportive documentation
- Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations
- Declined to provide documentation to support claim
- No communication response

Table 17. Manufacturer Response

Product Number	Communication Portals	Outcome
1	Email and Corporate Form	No communication response
2	Corporate Form	Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations
3	Email	Declined to provide documentation to support claim
4	Email	No communication response
5	Email	Provided supportive documentation[1]
6	Email	Declined to provide documentation to support claim
7	Corporate Form	No communication response
8	Email	No communication response
9	Corporate Form	No communication response
10	Email	Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations
11	Email	Provided supportive documentation
12	Email	Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations

[1] Company was unable to provide current clinical results as research was still ongoing and unavailable until 2018.

13	Email	No communication response

Based on our acquired responses, we looked at the calculated percent of overall responsive versus non-responsive, transparent versus non-transparent (declined to provide supportive data) within each company (refer to Table 18). Out of the thirteen (13) companies contacted, we observed a split in communication with 53.8% responsive and 46.2% non-responsive. Moreover, as we continued our correspondence, we discovered that responsiveness did not equate transparency. In fact, of the 53.8% responsive companies, only 15.4% were transparent and forthcoming with providing data while 38.5% responded and declined to provide data. While the significance of this finding may seem initially mundane, the importance of industry transparency to consumers is critical. If companies lose sight of their corporate responsibility of being the first stop to introduce an honest and transparent exchange regarding product information to patrons - then where can consumers go?

Table 18. Communication Response and Transparent Data

Product Number	Responsive	Non-responsive	Responsive + Transparent	Responsive + Non-transparent
1	X	✓	X	X
2	✓	X	X	✓
3	✓	X	X	✓
4	X	✓	X	X
5	✓	X	✓	X
6	✓	X	X	✓

7	X	✓	X	X
8	X	✓	X	X
9	X	✓	X	X
10	✓	X	X	✓
11	✓	X	✓	X
12	✓	X	X	✓
13	X	✓	X	X
Percent	**53.8**	**46.2**	**15.4**	**38.5**

Verifying Product Testing (In-house or Third Party)

Whether successful communication was established with each individual company, we proceeded with inquiring insight to the level of testing performed (internally or through third party laboratories) by evaluating company websites or identified studies.

If the company divulged into the type of testing performed, we proceeded to inquire whether basic (visual/observation, application, or smell), advanced analytical testing, or clinical studies were conducted relevant to product claim. We tabulated our findings based on the following response (refer to Table 19):

- Confirmed testing and provided supportive documentation
- Confirmed testing but declined to provide supportive data due to proprietary and commercially sensitive limitations.
- Declined to provide documentation to verify testing.
- No communication response

Table 19. Verifying Testing

Product Number	Testing Performed	Outcome
1	Testing Not Indicated on Corporate Website	No communication response
2	Testing Indicated on Corporate Website	Confirmed testing but declined to provide supportive data due to proprietary and commercially sensitive limitations.
3	Testing Not Indicated on Corporate Website	Declined to provide documentation to verify testing.
4	Clinical Studies Indicated on Corporate Website[2]	No communication response
5	Clinical Studies[3]	Provided supportive documentation
6	Testing Not Indicated on Corporate Website	Declined to provide documentation to verify testing.
7	Testing Not Indicated on Corporate Website	No communication response
8	Testing Not Indicated on Corporate Website	No communication response
9	Testing Indicated on Corporate Website	No communication response
10	Testing Not Indicated on Corporate Website	Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations
11	Testing Not Indicated on Corporate Website	Provided supportive documentation
12	Testing Not Indicated on Corporate Website	Declined to provide documentation to support claim due to proprietary and commercially sensitive limitations
13	Testing Not Indicated on Corporate Website	No communication response

We applied the same tabulation of our data transparency findings to product testing for each company. Based on our acquired responses, we looked at the overall

[2] (Biossance, 2017)

[3] Company was unable to provide current clinical results as research was still ongoing and unavailable until 2018.

percent of responsive versus unresponsive, transparent versus non-transparent (declined to provide supportive documentation of product testing) within each company Whether responsive or unresponsive, we included an additional column to categorize companies which indicated specific or nonspecific product testing transparency on their website (refer to Table 20).

Out of the thirteen (13) companies contacted, we observed a low percentage (23.1%) of companies indicated specific or nonspecific product testing transparency on their website. A staggering 76.9% of the companies did not indicate product testing on their website.

Over 50% of the companies we contacted failed to provide substantial transparency overall which is a significant finding in the age of open and public access to all consumers.

Table 20. Communication Response and Product Testing

Product Number	Non-responsive	Responsive + Transparent	Responsive + Non-transparent	Product Testing Indicated on Website	Product Testing Not Indicated on Website
1	✓	X	X	X	✓
2	X	X	✓	✓	X
3	X	X	✓	X	✓
4	✓	X	X	✓	X
5	X	✓	X	X	✓
6	X	X	✓	X	✓
7	✓	X	X	X	✓

8	✓	X	X	X	✓
9	✓	X	X	✓	X
10	X	X	✓	X	✓
11	X	✓	X	X	✓
12	X	X	✓	X	✓
13	✓	X	X	X	✓
Percent	**46.2**	**15.4**	**38.5**	**23.1**	**76.9**

Confirming Safety

While the business desirability for cosmeceutical companies to invest billions into science-based research products is certainly logical, its appeal stems partly due to minimal and less restrictive regulation compared to its traditional pharmaceutical counterpart. Currently, the FDA treats the cosmetics industry differently from the pharmaceutical drug industry – in that the cosmetic companies may use any ingredient in formulating products with the following caveat:

"In general, except for color additives and those ingredients that are prohibited or restricted by regulation, a manufacturer may use any ingredient in the formulation of a cosmetic, provided that:

- the ingredient and the finished cosmetic are safe under labeled or customary conditions of use
- the product is properly labeled
- the use of the ingredient does not otherwise cause the cosmetic to be adulterated or misbranded under the laws that FDA enforces" (U.S. Food & Drug Administration, 2013b).

Therefore, little effort is often made by manufacturers to substantiate clinical claims in an objective, scientific fashion. If we add the ever-changing consumer demographic and continual advancement in research technology to support this ever popular growth to "maintain youth", then it is clear why there is a massive incentive to cultivate cosmeceutical development. However, for the purpose of our study, we looked to confirm the minimum FDA requirements of safety and proper labeling practices.

Individual Ingredient Safety Evaluation and Function

The Cosmetic Ingredient Review (CIR) assessment was an essential arsenal when evaluating individual ingredient safety, cosmetic use, non-cosmetic use, clinical and toxicological relevance. Established in 1976, this organization is associated with the FDA, Consumer Federation of America, and the Personal Care Products Council. The CIR committee is composed of a dermatologist (from the American Academy of Dermatology), a toxicologist (from the Society of Toxicology), consumer representative (from the Consumer Federation of America), industry scientist, and various other industry specialists. The committee, itself, establishes procedures whose sole purpose is to determine and assess the safety of cosmetic ingredients based on intended use relevant to current research and clinical data.

The CIR (Section 30) follows a detailed annual procedure in order to provide complete ingredient safety assessment (Cosmetic Ingredient Review, 2010b) and classifies components per the following:

- Safe as currently used
- Safe with qualifications
- Unsafe
- Insufficient information for a determination (Cosmetic Ingredient Review, 2010b)

We reviewed all CIR assessments relevant to safety and established the following tables (refer to Table 42 and

Table 43):

Third Party: EWG Safety (Hazard and Data) Score

In addition, we utilized the Skin Deep® Cosmetic Database ("Skin Deep® Cosmetics Database," 2017a) scoring system to provide as an additional assessment of individual ingredient safety. Assessment and review of all ingredients established within the Skin Deep® Cosmetic Database is performed by EWG ("EWG," 2015), a third party organization.

We searched each product (as a whole) to determine whether it was automatically given a EWG Hazard and data score (refer to Figure 16). If the product (as a whole) was not pre-identified by EWG within the database, we manually populated each EWG score per EWG's Build Your Own Report (EWG, 2017) option for each unavailable product by

providing the required information. Our evaluated EWG safety and data score is presented in Table 21.

Table 21. EWG Product Safety Score (Hazard and Data)

Product Number	Automatic EWG Hazard Score	Manual EWG Hazard Score (Build Your Own Report)	Overall EWG Hazard Safety	Skin Deep® Cosmetic Database Data Availability
1	Not Identified	1	Safe	Fair
2	Not Identified	2	Safe	Limited
3	Not Identified	1	Safe	Limited
4	1	N/A	Safe	Limited
5	Not Identified	1	Safe	Limited
6	Not Identified	1	Safe	Limited
7	4	N/A	Safe	Limited
8	Not Identified	4	Safe	Limited
9	Not Identified	2	Safe	Limited
10	1	1	Safe	Fair
11	Not Identified	5	Safe	Limited
12	Not Identified	6	Safe	Limited
13	1	N/A	Safe	Limited

Evaluating Labeling

It is quite clear that guidance in establishing claim substantiation is relatively skewed with respect to the cosmeceutical industry. However, one established constant seems to apply not only with the cosmetic industry but with the drug industry as well - and that is proper labeling practices.

Therefore, in addition to ingredient and product safety, we reviewed all products to determine whether they complied with two basic governing labeling acts (refer to Table 9) - Federal Food, Drug, and Cosmetic (FD&C) Act and the Fair Packaging and Labeling (FP&L) Act. Our evaluated labeling assessment is presented in Table 44 and Table 45. If we were unable to complete our labeled assessment based on package images - we utilized the manufacturer's website to confirm overall compliance to the minimum requirements.

Tabulation of Research and Clinical Data

Once we've established exclusion of irrelevant ingredients for each product based on CIR safety assessments (refer to Table 42 and

Table 43); we reviewed all relevant ingredients applicable to product claims utilizing search engines such as PubMed, NIH, Toxnet, and ClinicalTrials. We cross referenced our product specific and ingredient specific terms with claim descriptive terms. We used the "advanced function" to optimize our results specific only to "title/abstract" featuring the term of interest, "title/abstract" featuring the claim descriptor, and "skin" searches - in order to reduce irrelevant search results (refer to Figure 18). Our findings are presented in Table 22 through Table 27.

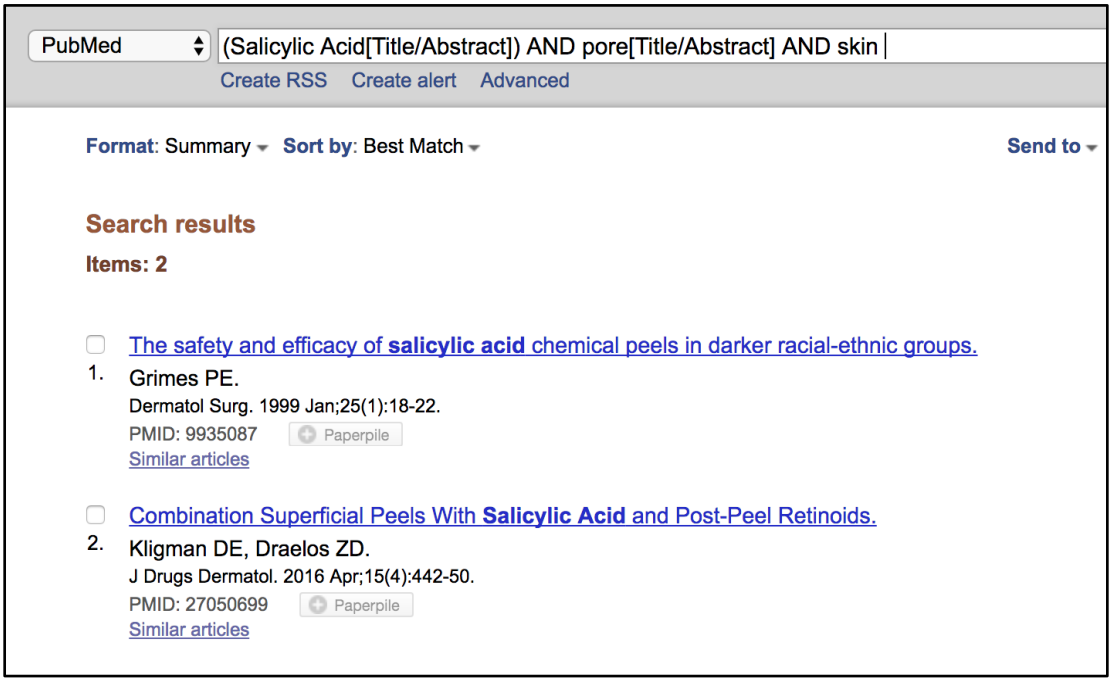


Figure 18. Example PubMed search

Table 22. Research Publication (Rose-Based Products)

Product Number	Primary Search Term	Relevant Claim Descriptor Search Term				Total Relevant Publications
		Claim #				
		1	2	3	4	
1		mattifying	minimizes pores	sebum control	shininess	0
	Rosa canina Fruit Extract	0	0	0	0	
2		cleans pores	controls sebum	exfoliates skin	normalizes cell turnover	22
	Limnanthes Alba (Meadowfoam) Seed Oil	0	0	0	0	
	Argania Spinosa Kernel Oil	0	0	0	0	
	Rosa Rubiginosa (Rose Hip) Seed Oil	0	0	0	0	
	Salicylic Acid	2	8	0	0	
	Serenoa Serrulata (Saw Palmetto) Fruit Extract	0	0	0	0	
	Leptospermum Scoparium Oil	0	0	0	0	
	Olea Europaea (Olive) Fruit Oil	0	0	0	0	
	Hippophae Rhamnoides Oil	0	1	0	0	
	Tocopheryl Acetate (Vitamin E)	0	11	0	0	
3		free radical protection	antioxidants	reduces fine lines	brightens	223
	Rosa Canina (Rosehip) Fruit Oil	0	0	0	0	
	Shea Butter Ethyl Esters	0	0	0	0	
	Citrus Aurantium Bergamia (Bergamot) Fruit Oil	0	0	0	0	
	Tocopheryl Acetate (Vitamin E)	56	164	3	0	
4		free radical protection	hydrates	reduces fine lines	brightens	0
	Squalane	0	0	0	0	
	Pistacia Lentiscus (mastic) Gum	0	0	0	0	
	Rosa Damascena Flower Extract	0	0	0	0	
5		balancing oil	vitamin E	low pH	fatty acid delivery	0
	Organic rosa canina (rosehip) fruit oil	0	0	0	0	
6		free radical protection	antioxidant	smooths fine lines	skin discoloration	321
	Rosehip (Rosa rubiginosa) oil	0	0	0	0	
	Ylang-Ylang (Cananga odorata) oil	0	1	0	0	
	Vitamin E (Tocopherols) oil	56	259	3	2	

Table 23. Research Publication (Silk-Based Products)

Product Number	Primary Search Term	Relevant Claim Descriptor Search Term				Total Relevant Publications
		Claim #				
		1	2	3	4	
7		moisturizes	smooths skin	skin texture	illuminates	1
	Cetyl Esters	0	0	0	0	
	C12-15 Alkyl Benzoate	0	0	0	0	
	Dimethicone	0	0	1	0	
	Hydrolyzed Silk	0	0	0	0	
8		anti-aging	skin cell regeneration	N/A	N/A	24
	Dimethicone	0	0	N/A	N/A	
	Silk Peptides	0	0	N/A	N/A	
	Avocado Oil	0	0	N/A	N/A	
	Ladys Mantle	0	0	N/A	N/A	
	Lemon Extract	0	0	N/A	N/A	
	Kinetin	8	0	N/A	N/A	
	Vitamin E	16	0	N/A	N/A	
9		antioxidant	moisturizing	N/A	N/A	287
	Butyrospermum Parkii (Shea Butter)	0	0	N/A	N/A	
	Cyclopentasiloxane	0	0	N/A	N/A	
	Theobroma Cacao (Cocoa) Seed Butter	2	0	N/A	N/A	
	C12-15 Alkyl Benzoate	0	0	N/A	N/A	
	Origanum Vulgare Leaf Extract	2	0	N/A	N/A	
	Cinnamomum Zeylanicum Bark Extract	0	1	N/A	N/A	
	Lavandula Angustifolia (Lavender) Flower Extract	3	0	N/A	N/A	
	Hydrastis Canadensis (Goldenseal) Root Extract	0	0	N/A	N/A	
	Hydrastis Canadensis (Goldenseal) Extract	0	0	N/A	N/A	
	Thymus Vulgaris (Thyme) Flower/Leaf Extract	1	1	N/A	N/A	
	Rosmarinus Officinalis (Rosemary) Leaf Extract	4	0	N/A	N/A	
	Lavandula Angustifolia (Lavender) Flower/Leaf/Stem Extract	3	0	N/A	N/A	
	Hydrolyzed Silk	0	0	N/A	N/A	
	Squalane	3	1	N/A	N/A	
	Tocopheryl Acetate (Vitamin E)	259	5	N/A	N/A	
	Simmondsia Chinensis (Jojoba) Seed Oil	0	0	N/A	N/A	
	Allantoin	2	0	N/A	N/A	
	Ethylhexylglycerin	0	0	N/A	N/A	
10		anti-aging	reduces wrinkles	reduces dark spots	brightens	14
	Silk	0	0	0	0	
	Vitamin C (L-ascorbic acid)	14	0	0	0	

Table 24. Research Publication (Silk+Rose Nano Combo Products)

Product Number	Primary Search Term	Relevant Claim Descriptor Search Term				Total Relevant Publications
		Claim #				
		1	2	3	4	
		anti-aging	reduces wrinkles	evens skin tone	antioxidants	
	Silk	0	0	0	1	
12	Vitamin C (Ascorbyl Glucoside)	14	0	3	107	126
	Sodium Anisate	0	0	0	0	
	Rosehip Oil	0	0	0	1	
		cellular renewal	hydration	absorbs toxins	antioxidants	
	Aloe Barbadensis (Aloe) Leaf Gel	0	3	0	1	
	Apricot Oil	0	0	0	0	
	Ascorbyl Palmitate	0	1	0	10	
	Coconut Oil	0	4	0	0	
	Glucose Oxidase	0	0	0	3	
	Jasmine Sambac Oil	0	0	0	0	
	Lactoperoxidase	0	0	0	0	
	Milk And Sugar Enzymes	0	0	0	0	
13	Retinyl	0	1	0	5	205
	Rosa Damascena Oil	0	0	0	0	
	Safflower Seed Certified Organic Oil	0	0	0	0	
	Sea Algae Extract	0	0	0	0	
	Silk Extract	0	0	0	0	
	Squalane	0	1	0	0	
	Tahitian Gardenia Oil	0	0	0	0	
	Tocopheryl Acetate (Vitamin E)	0	12	0	164	
	White Wine And Japanese Plum Extract	0	0	0	0	

Table 25. Clinical Trial Publication (Rose-Based Products)

Product Number	Primary Search Term	Relevant Claim Descriptor Search Term				Total Relevant Publications
		Claim #				
		1	2	3	4	
1		mattifying	minimizes pores	sebum control	shininess	0
	Rosa canina Fruit Extract	0	0	0	0	
2		cleans pores	controls sebum	exfoliates skin	normalizes cell turnover	7
	Limnanthes Alba (Meadowfoam) Seed Oil	0	0	0	0	
	Argania Spinosa Kernel Oil	0	0	0	0	
	Rosa Rubiginosa (Rose Hip) Seed Oil	0	0	0	0	
	Salicylic Acid	1	2	0	0	
	Serenoa Serrulata (Saw Palmetto) Fruit Extract	0	1	0	0	
	Leptospermum Scoparium Oil	0	0	0	0	
	Olea Europaea (Olive) Fruit Oil	0	0	0	0	
	Hippophae Rhamnoides Oil	0	0	0	0	
	Tocopheryl Acetate (Vitamin E)	0	3	0	0	
3		free radical protection	antioxidants	reduces fine lines	brightens	26
	Rosa Canina (Rosehip) Fruit Oil	0	0	0	0	
	Shea Butter Ethyl Esters	0	0	0	0	
	Citrus Aurantium Bergamia (Bergamot) Fruit Oil	0	0	0	0	
	Tocopheryl Acetate (Vitamin E)	5	19	2	0	
4		free radical protection	hydrates	reduces fine lines	brightens	0
	Squalane	0	0	0	0	
	Pistacia Lentiscus (mastic) Gum	0	0	0	0	
	Rosa Damascena Flower Extract	0	0	0	0	
5		balancing oil	vitamin E	low pH	fatty acid delivery	0
	Organic rosa canina (rosehip) fruit oil	0	0	0	0	
6		free radical protection	antioxidant	smooths fine lines	skin discoloration	39
	Rosehip (Rosa rubiginosa) oil	0	0	0	0	
	Ylang-Ylang (Cananga odorata) oil	0	1	0	0	
	Vitamin E (Tocopherols) oil	5	31	2	0	

Table 26. Clinical Trial Publication (Silk-Based Products)

Product Number	Primary Search Term	Relevant Claim Descriptor Search Term				Total Relevant Publications
		Claim #				
		1	2	3	4	
7		moisturizes	smooths skin	skin texture	illuminates	1
	Cetyl Esters	0	0	0	0	
	C12-15 Alkyl Benzoate	0	0	0	0	
	Dimethicone	0	0	0	0	
	Hydrolyzed Silk	0	1	0	0	
8		anti-aging	skin cell regeneration	N/A	N/A	3
	Dimethicone	0	0	N/A	N/A	
	Silk Peptides	0	0	N/A	N/A	
	Avocado Oil	0	0	N/A	N/A	
	Ladys Mantle	0	0	N/A	N/A	
	Lemon Extract	0	0	N/A	N/A	
	Kinetin	0	1	N/A	N/A	
	Vitamin E	2	0	N/A	N/A	
9		antioxidant	moisturizing	N/A	N/A	36
	Butyrospermum Parkii (Shea Butter)	0	0	N/A	N/A	
	Cyclopentasiloxane	0	0	N/A	N/A	
	Theobroma Cacao (Cocoa) Seed Butter	1	0	N/A	N/A	
	C12-15 Alkyl Benzoate	0	0	N/A	N/A	
	Origanum Vulgare Leaf Extract	0	0	N/A	N/A	
	Cinnamomum Zeylanicum Bark Extract	0	0	N/A	N/A	
	Lavandula Angustifolia (Lavender) Flower Extract	0	0	N/A	N/A	
	Hydrastis Canadensis (Goldenseal) Root Extract	0	0	N/A	N/A	
	Hydrastis Canadensis (Goldenseal) Extract	0	0	N/A	N/A	
	Thymus Vulgaris (Thyme) Flower/Leaf Extract	1	0	N/A	N/A	
	Rosmarinus Officinalis (Rosemary) Leaf Extract	0	0	N/A	N/A	
	Lavandula Angustifolia (Lavender) Flower/Leaf/Stem Extract	0	0	N/A	N/A	
	Hydrolyzed Silk	0	1	N/A	N/A	
	Squalane	1	1	N/A	N/A	
	Tocopheryl Acetate (Vitamin E)	31	0	N/A	N/A	
	Simmondsia Chinensis (Jojoba) Seed Oil	0	0	N/A	N/A	
	Allantoin	0	0	N/A	N/A	
	Ethylhexylglycerin	0	0	N/A	N/A	
10		anti-aging	reduces wrinkles	reduces dark spots	brightens	10
	Silk	0	0	0	0	
	Vitamin C (L-ascorbic acid)	2	5	3	0	
11		absorbs perspiration	cools	promotes skin balance	healthy scalp	0
	Silk (Serica) Powder	0	0	0	0	
	Linalool	0	0	0	0	
	Gentiana Lutea Root Extract	0	0	0	0	
	Quercus Robur Bark Extract	0	0	0	0	
	Salvia Officinalis (Sage) Leaf Extract	0	0	0	0	

Table 27. Clinical Trial Publication (Silk+Rose Nano Combo Products)

Product Number	Primary Search Term	Relevant Claim Descriptor Search Term				Total Relevant Publications
		Claim #				
		1	2	3	4	
		anti-aging	reduces wrinkles	evens skin tone	antioxidants	
	Silk	0	0	0	0	
12	Vitamin C (Ascorbyl Glucoside)	2	5	1	12	21
	Sodium Anisate	0	0	0	0	
	Rosehip Oil	0	1	0	0	
		cellular renewal	hydration	absorbs toxins	antioxidants	
	Aloe Barbadensis (Aloe) Leaf Gel	0	4	0	0	
	Apricot Oil	0	0	0	0	
	Ascorbyl Palmitate	0	0	0	1	
	Coconut Oil	0	2	0	0	
	Glucose Oxidase	0	0	0	0	
	Jasmine Sambac Oil	0	0	0	0	
	Lactoperoxidase	0	0	0	0	
13	Milk And Sugar Enzymes	0	0	0	0	33
	Retinyl	0	0	0	3	
	Rosa Damascena Oil	0	0	0	0	
	Safflower Seed Certified Organic Oil	0	0	0	0	
	Sea Algae Extract	0	0	0	0	
	Silk Extract	0	1	0	0	
	Squalane	0	0	0	0	
	Tahitian Gardenia Oil	0	0	0	0	
	Tocopheryl Acetate (Vitamin E)	0	3	0	19	
	White Wine And Japanese Plum Extract	0	0	0	0	

Influence of Patents and Third Party Certification

We performed a thorough review of relevant product-specific and ingredient-specific patents through the United States Patent and Trademark Office (USPTO) (United States Patent and Trademark Office, 2009), Google Patents Public Datasets (Google, 2017b), and World Intellectual Property Organization (WIPO) (WIPO, 2017). In our review of proprietary ingredients, we found a significant amount of patents filed relevant to ingredient-specific technology. Public access to patents may offer a supportive tool to consumers as they navigate the process of claim substantiation.

One company, for example, Silk Therapeutics®; offers an array of creams, serums, and cleansers that claim to promote the foundational benefits of liquid silk in

collaboration with other ingredients (such as coconut oil, lactic acid, and rosehip oil) (Silk Therapeutics, 2017a).

According to Silk Therapeutics' five (5) patent filings, the company established protection of their Silk Microcapsule™ technology (refer to Figure 19) that forms the basis for its array of skin care products (Altman et al, 2015). It is through this proprietary liquid silk technology (refer to Figure 20) that they claim to provide rapid release and penetration of antioxidant and anti-aging active ingredients into the skin.

The Silk Therapeutics® website, however, does not provide any evidence of supportive research or clinical data for any of their products but does include an ingredients list. Two such examples with ingredients which we have evaluated are the following Silk Therapeutics® products:

- SILK + C30 FILM with claims of "Diminishes the appearance of fine lines and wrinkles. Reduces the appearance of dark spots and uneven skin tone. Lifts, firms and brightens the appearance of skin" (Silk Therapeutics, 2017c) and two (2) ingredients listed: Silk and Vitamin C (L-ascorbic acid)
- Purely Smooth daily firming moisturizer with claims of "calming, evening skin tone, reducing the appearance of fine lines" and five (5) ingredients: water, silk, ascorbyl glucoside (Vitamin C), sodium anisate, and rosehip oil (Silk Therapeutics, 2017b).

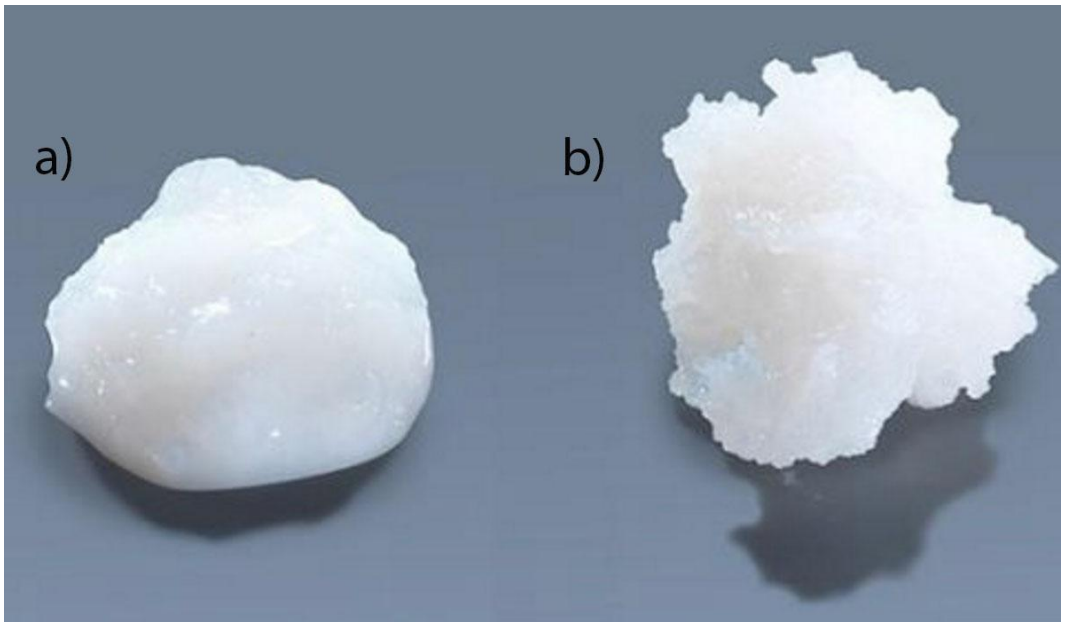


Figure 19. Silk Therapeutics® Microcapsule™ technology. a) Traditional cream formulation, b) Silk Microcapsule™ technology

Figure 20. Silk Therapeutics® liquid silk

Drug Claim Warning Letters Review

In October 2016, the FDA, provided a list of over fifty skin care companies that were given warning letters addressing misbranded drug claims made for products marketed as cosmetic (U.S. Food & Drug Administration, 2017b). Therefore, can it be safe to say that the cosmetic industry is not primarily technology or science driven but also undeniably marketing and claims driven? The more a product can claim to "enhance" or "protect" our skin/hair irrespective of its actual therapeutic capabilities – the stronger the desire to curate that product in one's beauty arsenal.

We reviewed the current list (as of August 2017) to determine if our evaluated companies or products were subject to receiving warning letters. We found that none of our selected companies and relating products were provided a warning letter in the years evaluated (2007-2017) (U.S. Food & Drug Administration, 2017b).

Final Claim Substantiation Scoring

After tabulating each criterion and ranking individual elements compared to our Product X baseline, our Pugh's matrix (refer to Table 28) reveals a substantial difference in claim substantiation - with the majority of the products receiving a low ranking or "unsupported claim substantiation" score based on Table 16.

Table 28. Final Pugh's Scoring Table

			Product Number													
Criteria	**Description**	**Weight (1-10)**	**Baseline (Product X)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Safety & Labeling	Safety	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Labeling	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Examining Products	Claims	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Ingredients	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
References	Product Specific	2	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ingredient Specific	5	0	-	+	+	-	-	+	0	+	+	+	-	+	+
Clinical	Product Specific	3	0	-	-	-	-	-	-	-	-	-	-	-	-	-
	Ingredient Specific	3	0	-	+	+	-	-	+	0	+	+	+	-	+	+
Product Testing	Manufacturer Information	5	0	-	0	-	0	0	-	-	-	0	-	0	-	-
Manufacturer Response	Manufacturer Information	3	0	-	-	-	-	0	-	-	-	-	-	0	-	-
Patents	Product Specific	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Ingredient Specific	1	0	0	0	0	0	0	0	+	0	0	+	0	0	+
Additional (Positive)	Third Party Certification	1	0	0	0	0	0	0	0	0	0	+	+	0	0	+
Additional (Negative)	Warning Letters (General Company)	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Warning Letters (Product Specific)	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Unidentified Ingredients	2	0	0	0	0	0	0	0	0	0	-	0	0	-	-
	Sum of (+)'s		0	0	2	2	0	0	2	1	2	3	4	0	2	4
	Sum of (-)'s		0	6	3	4	5	4	4	4	4	4	4	4	5	5
	Sum of (0)'s		16	10	11	10	11	12	10	11	10	9	8	12	9	7
	Weighted Sum Positives		0	0	8	8	0	0	8	1	8	9	10	0	8	10
	Weighted Sum Negatives		0	21	8	13	16	13	13	13	13	10	13	13	15	15
	Score: Weighted Positives - Weighted Negatives		0	-21	0	-5	-16	-13	-5	-12	-5	-1	-3	-13	-7	-5

Chapter IV

Discussion

One of the main motivations for conducting this research study was the desire to provide a thorough examination on the current regulatory landscape of the cosmeceutical industry. Currently, the FDA does not have a specific list of "acceptable" vs "non-acceptable" cosmetic claims. In fact, the FDA investigates the totality of the cosmetic label claims based on wording, imagery, and any promotional advertising. Therefore, it is a veritable wild wild west with respect to regulations. Moreover, implementing structural and codified changes within the traditional framework of the FDA may require a long and arduous process. Therefore, our study looked to provide a systematic methodology to improve the unmanageable noise that can stagnate regulatory improvements and processes.

While performing and conducting our research, it became clear that there were tremendous gaps to which regulatory, academic, and industry-relevant bodies lacked when looking to verify claim substantiation. We found the current unstandardized model to be both cumbersome and overwhelming. This gap was further amplified when we looked at it from a consumer's perspective with limitations to research and data access. In comparison, if we assess the opposite end of the spectrum, access to extensive "big data" can be problematic for even the most careful of regulating and industry professionals.

For instance, an obvious concern relevant to industry professionals is the selective filtering of statistically significant research and clinical data - unremoved from emotionally linked biases. How can one prevent the penchant for human preference and emotionally driven input from plaguing the quantification process?

Therefore, our aim was to to provide a remedy to this ongoing problem by summarizing the current governing standard and determine whether these provide reasonable guidance utilizing traditional federal regulatory agencies (such as the FDA, National Institute of Health [NIH], National Institute on Aging [NIA], Federal Trade Commission [FTC], National Advertising Department of the Better Business Bureau [NAD], and Consumer Product Safety Commission [CPSC]) and laws (such as the Food Drug and Cosmetic Act [FD&C], Fair Packaging & Labeling Act, and International Nomenclature of Cosmetic Ingredients (INCI). We evaluated and reviewed all approaches and portals with respect to data extraction in order to provide a thorough and cohesive evaluation for each stated claim with respect to individual ingredients and final product. As a result of our extensive review, we developed a quantifiable methodology to quickly determine (using quantifiable metrics) whether a product claim is substantiated.

In addition, our review looked to evaluate whether newly structured organizations (such as the FDA Nanotechnology Task Force or the Nanotechnology Industries Association) and Third Party certification organizations may provide specific direction toward future nano-cosmeceutical development utilizing the current governing standard. We included these additional components and Third Party organizations in order to

further differentiate companies (and their respective products) and provide additional quantifiable markers to our matrix.

Overall, our proposed method and matrix would establish a consistent process for producing robust and accurate claim substantiation. However, the following ongoing critical questions still need to be addressed with respect to matrix design:

- Do we evaluate products based as an overall therapeutic component or as individual ingredients?
- Do we regulate new nano-based cosmetic entities independently based on separate components?
- Are key authorities outside regulatory agencies needed to provide credible approval – such as physicians/dermatologists, scientists, and estheticians?

Company Transparency and Relationships

We unraveled significant insight to the growing need for standardized product testing and developed protocols for implementing claims substantiation within the cosmeceutical industry. One of the more interesting discoveries was uncovering the level of candidness to which most companies were at sharing data and product information - or rather the lack of candidness, in some cases. It was apparently clear that most companies did not uphold their promise to product transparency and corporate responsibility due to lack of regulatory enforcement. Therefore, will this behavior continue as social media and the drive of public opinion persists?

With the importance of consumer reviews through social media and the rise of public information via smart devices continues, the drive for ongoing discussion to seek truth in product claims will only persevere. In fact, we determined that claim

substantiation is not just purely based on research evidence alone - but also a collaborative synergy within the company and consumer based on transparency. How can we trust that our purchased product is safe and effective? Do we take a brand's word regarding its claims? If we begin by assuming a company has our best interests over its monetary and financial gains - it would serve us well to re-evaluate that level of trust and think again, as human greed can often trump all altruistic intentions. Today's consumers do not just arbitrarily read claims and make isolated decisions, however, they bring their past brand experiences and associations with them. This was a critical observation and one that lent implementation to our proposed methodology.

Therefore, one of the key components to our research was looking at product claim substantiation from a consumer's viewpoint. We found that consumers were limited to significant data access relevant to each product. In an ideal world, all individuals would have equal access to all published data - coupled with an open and transparent dialogue between most companies at a minimum. However, as we attempted to establish contact with each company (ranging from large to small size) with requests for additional information, we were met with minimal and often lackluster responses. In fact, out of the thirteen companies contacted we observed a split in communication, with 53.8% as responsive and 46.2% were non-responsive. And of the 53.8% responsive companies, only 15.4% were transparent and forthcoming with attempting to provide data while 38.5% responded and declined to provide data. Therefore, we can safely conclude that of the companies evaluated, only 15.4% were truly transparent. Which begs the question: do companies truly uphold their candid promise with respect to corporate

responsibility to the consumer? Or is it simply a half-hearted pledge to mislead the consumer into believing a faux relationship can be established? Where is the control? Whatever the case may be, it is certainly disheartening to uncover how substantial the power of marketing can influence public trust.

Limitations

As in any study, there are certain pitfalls that surface while undergoing any field of research due to time constraints or anomalies involving availability – such as accessibility to animal/clinical studies, proprietary ingredients or procedures, and limited access to data to general consumers.

Gaining insight in simply preventing symptoms of aging has become an active and lucrative area of interest for many biopharmaceutical and cosmetic companies. So the overwhelming desire to maintain youth and prevent the onset of degenerative signs of aging has become a fundamental research and business aim. Thus, the importance to regulate not only safety but truth in cosmetic claims which can often drive companies to create false products for monetary reward.

Future Expanse and Application

Further consideration for future studies would be to expand review of regulating bodies outside of the United States. With the world transforming into a space catered by

a socially customizable presence which dominates all industries, brands are expanding globally from all fronts. Evaluating European (EU) and Asian regulations may provide a more thorough guidance with respect to the cosmeceutical industry that has yet to transfer into the U.S. market. As our research only focused with the regulatory landscape of the U.S., future insight and studies inclusive of other world markets may provide as a fascinating extension.

The application of our methodology is not limited to the cosmetic or cosmeceutical industry alone. In fact, our developed matrix may be applied and used to investigate other industries including (but not limited to): supplements, packaged foods, nutraceuticals, and animal foods. The implementation of our modified Pugh's matrix method may assist as an in-process check for regulators, medical professionals in hospitals, and industry professionals before commercial product launch.

Conclusions

At the beginning of our study we looked to ask questions like: Do we evaluate products based as an overall therapeutic component, individual ingredients, or do we regulate new nano-based cosmetic entities independently based on separate components? We also looked to determine whether key authorities outside traditional regulatory agencies would provide approval and guidance. These are still ongoing questions that certainly need to be addressed and could provide added supportive insight to our decision making procedure in the future.

However, our current study examined natural extracts (such as rosa canina and rose-based oils), the value and use of natural fibers (such as the silk protein based nanoparticles), and reviewed the importance and trend toward its current marketable realm. We determined that it has only been in the past decade that use of these biomaterials have been broadened to examine new application strategies such as regenerative medicine, biomedical application, and beauty benefits. More specifically, silk proteins have been researched and examined in the realm of skin care due to its unique self-assembly, biocompatibility/biodegradability, mechanical properties, and enhanced functionality through chemical modification.

Overall, we found a significant gap with respect to regulatory access to industry professionals versus consumers. In addition, what little available influence consumers have with contacting manufacturers resulted in minimal (at best) transparency to available research conducted with respect to product claims.

Therefore, our proposed method and matrix may provide a novel systematic and unbiased approach at evaluating a nano-cosmeceutical compound relative to claims substantiation looking at a range of evidence based criteria:

1) Assess overall claim(s) of the product/company
2) Provide a list of major ingredients that are relevant to product claim(s)
3) Evaluate evidence based data through:
    - Patents
    - Published scientific literature and clinical data (PubMed, NIH, TOXNET)
    - Company website verbiage and communication confirming ingredient applicability
    - Product and ingredient-specific testing
    - Third party certification
    - Regulatory warning letters

Our study assessed that the FDA and FD&C Act provide cursory oversight regarding the acceptable boundaries of intended use claims for cosmetic products and therapeutic drugs - with clear standards still remaining obscure. For instance, a stated claim can have differing meaning relative to the interpreter and how it is implied. We found some of the bulk of FDA's guidance extracted from a careful review of observations set forth in Warning Letters issued. However, overall direction in clarifying cosmetic claims which bear striking similarities to therapeutic drug claims is still in its infancy. Our methodology would provide the necessary impact at optimizing the inadequate regulatory landscape which governs the cosmeceutical industry and overall claims validation.

In the end, having the necessary and available tools to make educated decisions on products claim substantiation is critical. Consumers should be confident that product claims are substantiated and held to a defined standard or regulation when making their purchase. Ultimately, knowing what the product does is pivotal but discerning whether these critical claim attributes are legitimized will help improve decision-making and consumer buying power.

Appendix

Additional Figures

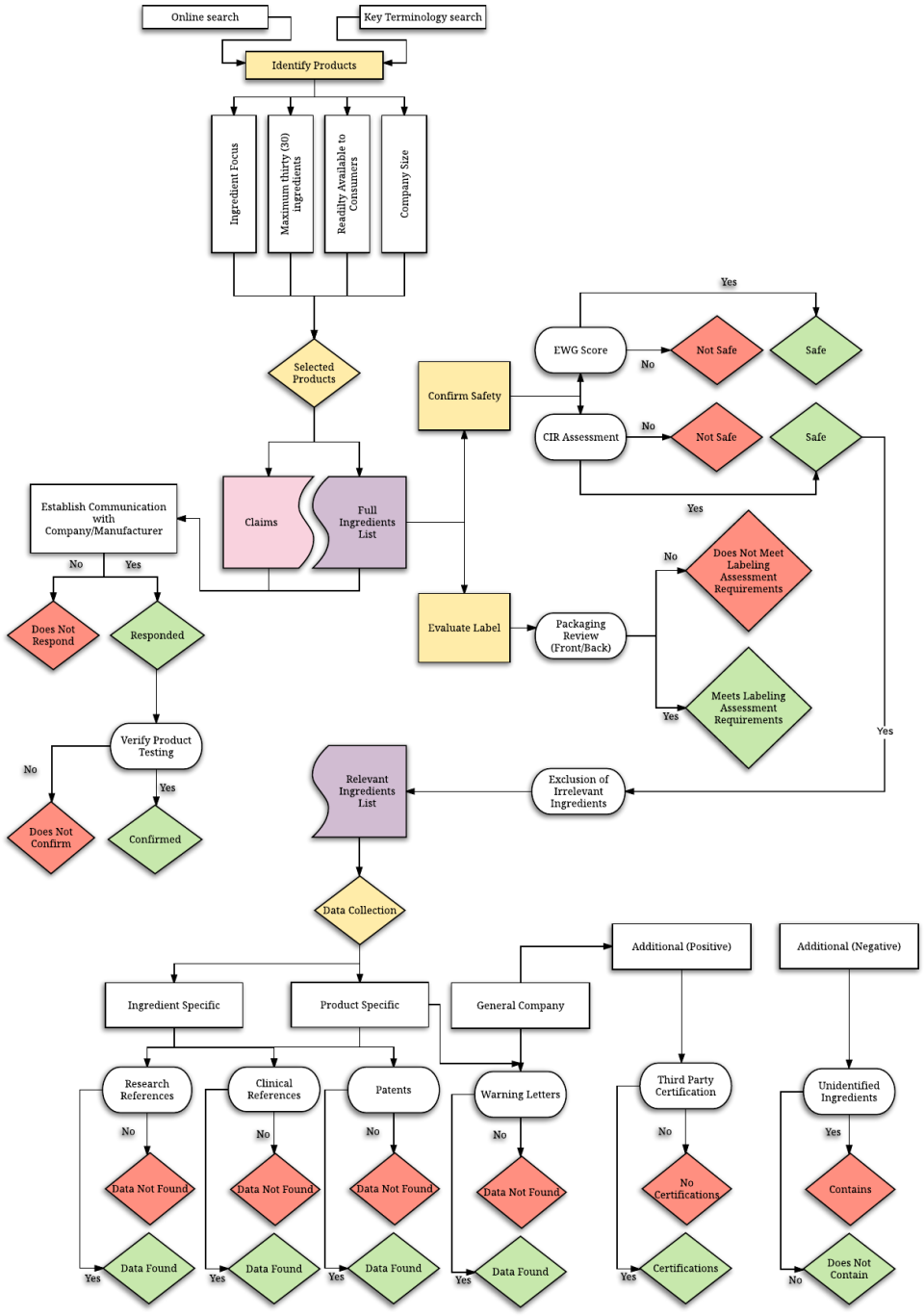


Figure 21. Methodology Flow Chart

Additional Tables

Table 29. Safety and Labeling Criteria

Safety and Labeling	Score
Safety: Criticality of product safety	
Higher impact of product safety than baseline product	+
Lower impact of patient safety than baseline product	-
Baseline product or same impact to product safety as baseline product	0
Labeling (FD&C Act; Sec 301 and 602): Criticality of establishing proper labeling requirements	
Higher impact to establishing proper labeling as baseline product	+
Lower impact to establishing proper labeling as baseline product	-
Baseline product or same impact to establishing proper labeling as baseline product	0

Table 30. Examining Products Criteria

Examining Products	Score
Claims: Provide reasonable claim	
Higher amount of reasonable claims provided as compared to baseline product	+
Lower amount of reasonable claims provided as compared to baseline product	-
Baseline product or same amount of reasonable claims provided as compared to baseline product	0
Ingredients: Include full ingredient list on packaging	
Higher impact to include ingredient list as baseline product	+
Lower impact to include ingredient list as baseline product	-
Baseline product or same impact to include ingredient list as baseline product	0

Table 31. References Criteria

References	Score
Product Specific: Provide at least one research publication that supports product claim.	
Higher impact to establishing at least one reference as baseline product	+
Lower impact to establishing at least one reference as baseline product	-
Baseline product or same impact to establishing at least one reference as baseline product	0
Ingredient Specific: Provide at least one research publication that supports product claim.	
Higher impact to establishing at least one reference as baseline product	+
Lower impact to establishing at least one reference as baseline product	-
Baseline product or same impact to establishing at least one reference as baseline product	0

Table 32. Clinical Criteria

Clinical	Score
Product Specific: Provide at least one clinical study that supports product claim.	
Higher impact to establishing at least one clinical study as baseline product	+
Lower impact to establishing at least one clinical study as baseline product	-
Baseline product or same impact to establishing at least one clinical study as baseline product	0
Ingredient Specific: Provide at least one clinical study that supports product claim.	
Higher impact to establishing at least one clinical study as baseline product	+
Lower impact to establishing at least one clinical study as baseline product	-
Baseline product or same impact to establishing at least one clinical study as baseline product	0

Table 33. Product Testing Criteria

Product Testing	Score
Manufacturer Information: Confirms claim specific testing	
Manufacturer confirms testing and provides supportive documentation	+
Manufacturer declines to provide documentation to verify testing	-
No communication response from manufacturer	-
Baseline product or same impact to confirms claim specific testing as baseline product	0
Manufacturer confirms testing but declines to provide supportive data due to proprietary and commercially sensitive limitations	0

Table 34. Manufacturer Response Criteria

Manufacturer Response	Score
Manufacturer Information: Provide full communication and transparency to academic/industry/beauty professionals and consumers	
Manufacturer provides full communication and provides supportive documentation	+
Manufacturer declines to provide supportive documentation	-
No communication response from manufacturer	-
Baseline product or same impact to provide full communication and transparency to academic/industry/beauty professionals and consumers	0
Manufacturer responses but declines to provide supportive data due to proprietary and commercially sensitive limitations	0

Table 35. Patents

Patents	Score
Product Specific	
Higher amount of product specific patents provided as compared to baseline product	+
Lower amount of product specific patents provided as compared to baseline product	-
Baseline product or same amount of product specific patents provided as compared to baseline product	0
Ingredient Specific	
Higher amount of ingredient specific patents provided as compared to baseline product	+
Lower amount of ingredient specific patents provided as compared to baseline product	-
Baseline product or same amount of ingredient specific patents provided as compared to baseline product	0

Table 36. Additional (Positives) - Third Party Certification

Additional (Positives)	Score
Third Party Certification	
Higher amount of third party certification provided as compared to baseline product	+
Lower amount of third party certification provided as compared to baseline product	-
Baseline product or same amount of third party certification provided as compared to baseline product	0

Table 37. Additional (Negatives) - Warning Letters & Unidentified Ingredients

Additional (Negatives)	Score
Regulatory Warning Letters (General Company)	
Higher amount of regulatory warning letters provided as compared to baseline product	-
Lower amount of regulatory warning letters provided as compared to baseline product	+
Baseline product or same regulatory warning letters provided as compared to baseline product	0
Regulatory Warning Letters (Product Specific)	
Higher amount of product specific regulatory warning letters provided as compared to baseline product	-
Lower amount of product specific regulatory warning letters provided as compared to baseline product	+
Baseline product or same amount of product specific regulatory warning letters provided as compared to baseline product	0
Unidentified Ingredients	
Higher amount of unidentified or irrelevant ingredients provided as compared to baseline product	-
Lower amount of unidentified or irrelevant ingredients provided as compared to baseline product	+
Baseline product or same amount of unidentified or irrelevant ingredients provided as compared to baseline product	0

Table 38. Collected Product List

Product Type	Product Number	Company Size[4]	Company Name	Product Name
Rose	1	L	Silab	Sebocytine (Silab, 2017)
	2	L	Bobbi Brown Cosmetics (Estee Lauder Company)	SKIN CLARIFIER NO. 75 PORE & OIL CONTROL (Bobbi Brown Cosmetics, 2017)
	3	M	Julep	Boost Your Radiance (Biossance, 2017)
	4	M	Biossance (Amyris, Inc)	Squalane + Vitamin C Rose Oil (Biossance, 2017)
	5	S	Acure Organics (Better Planet Brands LLC)	Rosehip Oil (Acure Organics, 2017)
	6	S	Odacite Skincare	Ro+Y | Deep Wrinkles (Odacite, 2017)
Silk	7	L	Jergens (Kao Corporation)	Daily Moisture Fragrance Free Moisturizer (Jergens, 2015)
	N/A[5]	L	None Identified	None Identified
	8	M	OFRA Cosmetic Laboratories	Peptide Silk-C Serum (Ofra Cosmetics, 2017)
	9	M	PCA Skin	Silkcoat Balm (PCA Skin, 2017)
	10	S	Silk Therapeutics	SILK + C30 FILM (Silk Therapeutics, 2017c)
	11	S	Dr. Hauschka Skin Care, Inc.	Silk Body Powder (Dr. Hauschka, 2017)
Rose+Silk Nano Combo	N/A[2]	L	None Identified	None Identified
	N/A[2]	L	None Identified	None Identified
	N/A[2]	M	None Identified	None Identified

[4] Company Size: Large (L), Medium (M), Small (S)

[5] Product not identified due to lack of availability based on four categories for product selection.

	N/A[2]	M	None Identified	None Identified
	12	S	Silk Therapeutics	PURELY SMOOTH (Silk Therapeutics, 2017b)
	13	S	Red Flower	plum blossom silk cream (Red Flower, 2017)

Table 39. Full Ingredient List

Product #	Full List of Ingredients		
1	❑ Water	❑ Butylene Glycol	❑ **Rosa canina Fruit Extract**
2	❑ Limnanthes Alba (Meadowfoam) Seed Oil ❑ Argania Spinosa Kernel Oil ❑ **Rosa Rubiginosa (Rose Hip) Seed Oil**	❑ Salicylic Acid ❑ Serenoa Serrulata (Saw Palmetto) Fruit Extract ❑ Leptospermum Scoparium Oil	❑ Olea Europaea (Olive) Fruit Oil ❑ Hippophae Rhamnoides Oil ❑ Tocopheryl Acetate (Vitamin E)
3	❑ **Rosa Canina (Rosehip) Fruit Oil** ❑ Shea Butter Ethyl Esters	❑ Citrus Aurantium Bergamia (Bergamot) Fruit Oil ❑ Tocopheryl Acetate (Vitamin E)	
4	❑ Squalane ❑ Pistacia Lentiscus (mastic) Gum	❑ **Rosa Damascena Flower Extract** ❑ Tetrahexyldecyl Ascorbate	❑ Caprylic/Capric Triglycerides
5	❑ **Rosa canina (rosehip) fruit oil**		
6	❑ **Rosehip (Rosa rubiginosa) oil**	❑ Ylang-Ylang (Cananga odorata) oil	❑ Vitamin E (Tocopherols) oil
7	❑ Water ❑ Glycerin ❑ Cetearyl Alcohol ❑ Cetyl Esters ❑ Ceteareth-20 ❑ Cetyl Alcohol	❑ Glyceryl Dilaurate ❑ Mineral Oil ❑ C12-15 Alkyl Benzoate ❑ Dimethicone ❑ Stearic Acid	❑ DMDM Hydantoin ❑ Methylparaben ❑ Isopropyl Myristate ❑ Propylparaben, Carbomer ❑ Sodium Hydroxide ❑ **Hydrolyzed Silk**
8	❑ Water ❑ Cetearyl Alcohol And Sodium Cetearyl Sulfate ❑ Capric/Caprylic Triglycerides ❑ Glycerin ❑ Propylene Glycol ❑ Decyl Oleate ❑ Dimethicone	❑ Hyaluronic Acid ❑ Tetrahexyldecyl Ascorbate ❑ **Silk Peptides** ❑ Avocado Oil ❑ Polyacrylamide & C13-14 Isoparaffin & Laureth-7 ❑ Ladys Mantle	❑ Lemon Extract ❑ Kinetin ❑ Phenoxy Ethanol ❑ Vitamin E ❑ Fragrance ❑ Fd&C Yellow #7
9	❑ Water/Aqua/Eau ❑ Glycerin ❑ Butyrospermum Parkii (Shea Butter) ❑ Caprylic/Capric Triglyceride ❑ Cetyl Alcohol, Glyceryl Stearate ❑ Dimethicone ❑ Cyclopentasiloxane ❑ Theobroma Cacao (Cocoa) Seed Butter ❑ C12-15 Alkyl Benzoate ❑ Stearic Acid ❑ Potassium Cetyl Phosphate	❑ Cetearyl Alcohol ❑ Polysorbate 60 ❑ Origanum Vulgare Leaf Extract ❑ Cinnamomum Zeylanicum Bark Extract ❑ Lavandula Angustifolia (Lavender) Flower Extract ❑ Hydrastis Canadensis (Goldenseal) Root Extract ❑ Hydrastis Canadensis (Goldenseal) Extract ❑ Thymus Vulgaris (Thyme) Flower/Leaf Extract ❑ Rosmarinus Officinalis (Rosemary) Leaf Extract ❑ Lavandula Angustifolia (Lavender) Flower/Leaf/Stem Extract	❑ **Hydrolyzed Silk** ❑ Squalane ❑ Tocopheryl Acetate ❑ Simmondsia Chinensis (Jojoba) Seed Oil ❑ Allantoin ❑ Phenoxyethanol ❑ Ethylhexylglycerin ❑ Acrylates/C10-30 Alkyl Acrylate Crosspolymer ❑ Sodium Hydroxide
10	❑ **Silk**	❑ Vitamin C (L-ascorbic acid)	
11	❑ Oryza Sativa (Rice) Starch ❑ **Silk (Serica) Powder** ❑ Silica ❑ Fragrance (Parfum) ❑ Linalool	❑ Limonene ❑ Geraniol ❑ Coumarin ❑ Citronellol ❑ Citral	❑ Gentiana Lutea Root Extract ❑ Quercus Robur Bark Extract ❑ Salvia Officinalis (Sage) Leaf Extract ❑ Diatomaceous Earth (Solum Diatomeae)
12	❑ Water ❑ **Silk**	❑ Vitamin C (Ascorbyl Glucoside) ❑ Sodium Anisate	❑ **Rosehip Oil**
13	❑ Alcohol Certified Organic ❑ Aloe Barbadensis (Aloe) Leaf Gel ❑ Apricot Oil ❑ Ascorbyl Palmitate ❑ Coconut Oil ❑ Glucose Oxidase ❑ Jasmine Sambac Oil ❑ Lactoperoxidase	❑ Milk And Sugar Enzymes ❑ Potassium Sorbate, Retinyl ❑ **Rosa Damascena Oil** ❑ Safflower Seed Certified Organic Oil ❑ Sea Algae Extract ❑ **Silk Extract** ❑ Soft-Water	❑ Squalane ❑ Tahitian Gardenia Oil ❑ Tocopheryl Acetate ❑ Vegetable Glycerin ❑ Vegetable-Derived Emulsifying Wax ❑ White Wine And Japanese Plum Extract ❑ Xanthan Gum

Table 40. Claims (Rose-based Products)

Product #	General Claims	Ingredient Specific Claims	Clinical/Statistical Claims
1	❑ Slowing the rate of sebum secretion ❑ Reducing pore size ❑ Limits shininess and imperfections of the skin. ❑ Mattifying power has been demonstrated.	NL	NL
2	❑ Cleans out pores ❑ Controls sebum ❑ Normalized cell turnover ❑ Gently exfoliates and refines skin ❑ Balances skin ❑ Creates a healthy skin environment	❑ Manuka, Seabuckthorn and Rosehip oils: Help balance sebum levels and create a healthy skin environment. ❑ Salicylic Acid: Helps remove pore-clogging debris and purify blemish-prone skin for a more refined complexion.	❑ 90% said it left skin more balanced after 4 weeks ❑ 92% said it left skin looking more refined after 4 weeks ❑ 88% said it helped improve the appearance of pore-clogged skin after 4 weeks ❑ 88% said it minimized the appearance of pores after 4 weeks ❑ 81% said it left skin with a natural, shine-free appearance after 4 weeks
3	❑ Leaves all skin types radiant and hydrated. ❑ Prevents and repairs the appearance of fine lines and hyperpigmentation while regulating oil production.	❑ Vitamin E: Aids in the absorption of the rosehip seed oil. Protects against free radical damage with antioxidants ❑ Rosehip Seed Oil: Reduces the appearance of fine lines, scars and hyperpigmentation. Contains healing and regenerating properties. Regulates oil production while moisturizing. ❑ Bergamot Oil: Contains brightening benefits. Has natural antiseptic properties	NL
4	❑ Brightens with an oil soluble, stable form of Vitamin C, 50x more powerful than ascorbic acid ❑ Fights free radicals and leaves skin with a healthy-looking radiance ❑ Reduces the appearance of fine lines and wrinkles	❑ Squalane: Instantly hydrates while locking in essential moisture ❑ Vitamin C: Helps fight free radicals with 50x the brightening power of ascorbic acid, leaving skin with a radiant glow ❑ Chios Crystal Oil: Shown to support collagen production, to leave skin looking firm and feeling supple ❑ Damascus Rose Extract: Awakens the senses, relieving daily stressors and boosting radiance	❑ 97% agree skin suppleness and firmness is improved ❑ 91% agree skin has a healthy radiant glow ❑ 32% increase in skin radiance
5	Same as Ingredient Specific Claims	❑ Rosehip oil is known as a balancing oil due to it's low pH to help protect the skin's natural acid mantle while delivering essential fatty acids and vitamin E. ❑ Cold-pressed rose fruit seeds (or the hips) make this known as a dry oil due to its quick absorption.	NL
6	❑ Super regenerative serum concentrated with potent bio-actives that help to reverse wrinkles & smooth out facial lines while improving skin discoloration.	❑ One of the most regenerative oils, Rosehip is rich in vitamin C known to boost collagen, providing the skin with the support it needs to stay firm and healthy. ❑ Rosehip synergistically pairs with Ylang-Ylang to enhance antioxidant activity, helping to reverse free-radical damage and slow down the aging process.	NL

Table 41. Claims (Silk and Rose+Silk Nano-based Products)

Product #	General Claims	Ingredient Specific Claims	Clinical/Statistical Claims
7	❑ Instantly moisturizes rough, dry skin to reveal skin that's deeply radiant and 4x as smooth, without a fragrance. ❑ Provides continuous multi-layer moisture to smooth skin and improve its tone, texture, and luminosity. ❑ Locks in moisture for up to 24 hours.	❑ Smoothes rough, dry skin. With a unique illuminating HYDRALUCENCE™ blend and Silk Proteins.	Not Listed
8	❑ Peptide base designed to help hydrate the skin producing significant anti-aging results. ❑ Men and women of any skin tone will experience dramatic results complimenting the products high quality ingredients.	❑ Includes Kinetin, a plant hormone, to promote regeneration of skin cells. ❑ Peptide Silk-C Serums complex incorporates matchless ingredients, each enhancing the product by providing a number of benefits. Among them: Silk Peptides, Hyaluronic Acid, Kinetin, Vitamin C, Ladys Mantle and Lemon Extract.	Not Listed
9	❑ Silk protein provides deep, non-greasy moisture ❑ Potent antioxidant protection ❑ Helps calm and improve the appearance of aging skin ❑ Formulated with antioxidants, botanicals and hydrolyzed silk, this moisturizer is the ultimate treatment for dry and mature skin, and skin in harsh or cold climates.	❑ Jojoba seed oil: A natural ingredient with moisturizing properties. ❑ Hydrolyzed silk: A light, non-greasy moisturizer and skin conditioner. ❑ Vitamin E: A powerful antioxidant. ❑ Squalane: Naturally occurring in olives and wheat germ, this ingredient keeps skin moist.	Not Listed
10	❑ Anti-aging treatment - an ultra concentrated, dissolving film comprised of only activated liquid silk and 30% vitamin C - targets specific problem areas with immediate results. ❑ Diminishes the appearance of fine lines and wrinkles ❑ Reduces the appearance of dark spots and uneven skin tone ❑ Lifts, firms and brightens the appearance of skin	Same as General Claims	Before and After Picture Provided On Website
11	❑ Maintains the skin's healthy pH balance and absorbs perspiration, naturally helping to neutralize odors.	❑ Silk powder is nearly the same protein composition as the skin, making for easy compatibility. ❑ Gentian and oak extracts cool and refresh. ❑ Sage extract supports healthy skin and scalp.	Not Listed
12	❑ Anti-aging serum-moisturizer is formulated with Silk Microcapsule™ technology, vitamin C, and potent antioxidants to both hydrate and treat the skin. ❑ Diminishes the appearance of fine lines and wrinkles ❑ Evens skin tone ❑ Lifts and firms the appearance of skin	Same as General Claims	Before and After Picture Provided On Website
13	❑ Hydrate, protect, soften complete the feeling of soft skin with a delicate, protective layer of silk. ❑ Highly-absorbent, nutritive cream is a blend of rose blossoms, concentrated silk extracts and plum wine serum.	❑ Whole rose essential oil is filled with vitamins a, c, and e to heal skin and restore suppleness. ❑ Plum wine serum is a natural, gentle, skin replenishing sugar acid that encourages cellular renewal. ❑ Concentrated silk extract to protect against drying elements and enrich the skin with ten hours of healing hydration. ❑ Silk powder can protect from loss of moisture and absorb toxins depending on the temperature and humidity along the skin's surface. an ample source of anti-oxidants, protein and amino acids, silk powder has long been a treasured ingredient in the quest for flawless perfection.	Not Listed

Table 42. CIR Safety Classification and Function (Rose)

Product Number	Ingredients	CIR Safety Class[6]	Function[7]	Reference
1	Water	NA	SO	N/A
	Butylene Glycol	S	E; SO	(CIR, 1985)
	Rosa canina Fruit Extract	S	SC	(CIR, 2017e)
2	Limnanthes Alba (Meadowfoam) Seed Oil	S	SC	(CIR, 2011c)
	Argania Spinosa Kernel Oil	S	SC	(CIR, 2011c)
	Rosa Rubiginosa (Rosehip) Seed Oil	S	SC	(CIR, 2016f)
	Salicylic Acid	S	SC	(CIR, 2003c)
	Serenoa Serrulata (Saw Palmetto) Fruit Extract	NA	SC	N/A
	Leptospermum Scoparium Oil	NA	F	N/A
	Olea Europaea (Olive) Fruit Oil	S	SC	(CIR, 2011c)
	Hippophae Rhamnoides Oil	S	SC	(CIR, 2011c)
	Tocopheryl Acetate (Vitamin E)	S	AO; SC	(CIR, 2014c)
3	**Rosa Canina (Rosehip) Fruit Oil**	S	SC	(CIR, 2017e)
	Shea Butter Ethyl Esters	S	SC	(CIR, 2016f)
	Citrus Aurantium Bergamia (Bergamot) Fruit Oil	S	F; SC	(CIR, 2016a)
	Tocopheryl Acetate (Vitamin E)	S	AO; SC	(CIR, 2014c)
4	Squalane	S	SC	(CIR, 2003a)
	Pistacia Lentiscus (mastic) Gum	NA	AD; F	N/A
	Rosa Damascena Flower Extract	NA	F	N/A
	Tetrahexyldecyl Ascorbate	S	F; AO; SC; SB	(CIR, 2017c)
	Caprylic/Capric Triglycerides	S	F; SC	(CIR, 2003a)
5	**Organic rosa canina (rosehip) fruit oil**	S	SC	(CIR, 2011c)
6	**Rosehip (Rosa rubiginosa) oil**	S	SC	(CIR, 2016f)
	Ylang-Ylang (Cananga odorata) oil	NA	F	N/A

[6] CIR Classification: S=Safe, U=Unsafe, NA=No Assessment

[7] Function: SO=Solvent, SC=Skin Conditioning, F=Fragrance, AD=Adhesive, AO=Antioxidant, SB=Skin Bleaching, V=Viscosity, E=Emulsifier, SU=Surfactant, SP=Skin Protecting, AM=Antimicrobial, P=Preservative, DN=Denaturant, PH=pH Adjuster, BU=Buffering, CL=Cleansing, BI=Binding, AS=Astringent, DO=Deodorant, H=Humectant, NR=Not Reported.

	Vitamin E (Tocopherols) oil	S	AO; SC	(CIR, 2014c)

Table 43. CIR Safety Classification and Function (Silk, Silk + Rose Nano Combo)

Product Number	Ingredients	CIR Safety Class[8]	Function[9]	Reference
7	Water	NA	SO	N/A
	Glycerin	S	F; SC; V	(CIR, 2015b)
	Cetearyl Alcohol	S	E; V	(CIR, 2008a)
	Cetyl Esters	S	AO; C	(CIR, 2015a)
	Ceteareth-20	S	SU; SC;	(CIR, 2012b)
	Cetyl Alcohol	S	F; SC; V	(CIR, 2008a)
	Glyceryl Dilaurate	S	E; SC	(CIR, 2007a)
	Mineral Oil	NA	F; SC; SP	N/A
	C12-15 Alkyl Benzoate	S	SC; AM	(CIR, 2012a)
	Dimethicone	S	SC SP	(CIR, 2003b)
	Stearic Acid	S	F; SU; E	(CIR, 2006b)
	DMDM Hydantoin	S	P	(CIR, 2008a)
	Methylparaben	S	F; P	(CIR, 2008b)
	Isopropyl Myristate	S	F; SO; SC	(CIR, 2015a)
	Propylparaben	S	F; P	(CIR, 2008b)
	Carbomer	S	E; V	(CIR, 2003a)
	Sodium Hydroxide	S	DN; PH; BU	(CIR, 2016b)
	Hydrolyzed Silk	S	SC	(CIR, 2016g)
8	Water	NA	SO	N/A
	Cetearyl Alcohol	S	E; V	(CIR, 2008a)
	Sodium Cetearyl Sulfate	S	SU; CL	(CIR, 2010b)

[8] CIR Classification: S=Safe, U=Unsafe, NA=No Assessment

[9] Function: SO=Solvent, SC=Skin Conditioning, F=Fragrance, AD=Adhesive, AO=Antioxidant, SB=Skin Bleaching, V=Viscosity, E=Emulsifier, SU=Surfactant, SP=Skin Protecting, AM=Antimicrobial, P=Preservative, DN=Denaturant, PH=pH Adjuster, BU=Buffering, CL=Cleansing, BI=Binding, AS=Astringent, DO=Deodorant, H=Humectant, NR=Not Reported

	Capric/Caprylic Triglycerides	S	F; SC	(CIR, 2003a)
	Propylene Glycol	S	F; SC; SO; V	(Fiume MM, n.d.)
	Decyl Oleate	S	SC; E	(CIR, 2015a)
	Dimethicone	S	SC; SP	(CIR, 2003b)
	Hyaluronic Acid	S	SC; V	(CIR, 2009a)
	Glycerin	S	F; SC; V	(CIR, 2015b)
	Tetrahexyldecyl Ascorbate	S	F; AO; SC; SB	(CIR, 2017d)
	Silk Peptides	S	SC	(CIR, 2016g)
	Avocado Oil	S	F; P	(CIR, 2011c)
	Polyacrylamide	S	BI	(CIR, 2005a)
	C13-14 Isoparaffin	S	SO	(CIR, 2012c)
	Laureth-7	S	SU; E	(CIR, 2012b)
	Ladys Mantle	NA	SC; AS	N/A
	Lemon Extract	S	F; SC	(CIR, 2016a)
	Kinetin	NA	SC	N/A
	Phenoxy Ethanol	S	F; P	(CIR, 2011a)
	Vitamin E	S	AO; SC	(CIR, 2014c)
	Fragrance	NA	F	N/A
	Fd&C Yellow #7	NA	C	N/A
9	Water/Aqua/Eau	NA	SO	N/A
	Glycerin	S	F; SC; V	(CIR, 2015b)
	Butyrospermum Parkii (Shea Butter)	S	SC; V	(CIR, 2017a)
	Caprylic/Capric Triglyceride	S	F; SC	(CIR, 2003a)
	Cetyl Alcohol	S	F; SC; V	(CIR, 2008a)
	Glyceryl Stearate	S	SU; E	(CIR, 2016e)
	Dimethicone	S	SC; SP	(CIR, 2003b)
	Cyclopentasiloxane	S	SC	(CIR, 2011d)

	Theobroma Cacao (Cocoa) Seed Butter	S	F; SC; SP	(CIR, 2011c)
	C12-15 Alkyl Benzoate	S	SC; AM	(CIR, 2012a)
	Stearic Acid	S	F; SU; E	(CIR, 2006b)
	Potassium Cetyl Phosphate	S	SU; E	(CIR, 2014a)
	Cetearyl Alcohol	S	E; V	(CIR, 2008a)
	Polysorbate 60	S	F; SU; E	(CIR, 2015c)
	Origanum Vulgare Leaf Extract	NA	SC	N/A
	Cinnamomum Zeylanicum Bark Extract	NA	SC	N/A
	Lavandula Angustifolia (Lavender) Flower Extract	NA	F	N/A
	Hydrastis Canadensis (Goldenseal) Root Extract	NA	NR	N/A
	Hydrastis Canadensis (Goldenseal) Extract	NA	NR	N/A
	Thymus Vulgaris (Thyme) Flower/Leaf Extract	NA	F; SC; SP	N/A
	Rosmarinus Officinalis (Rosemary) Leaf Extract	S	AM; AO; F; SC	(CIR, 2014b)
	Lavandula Angustifolia (Lavender) Flower/Leaf/Stem Extract	NA	F	N/A
	Hydrolyzed Silk	S	SC	(CIR, 2016g)
	Squalane	S	SC	(CIR, 2003a)
	Tocopheryl Acetate	S	AO; SC	(CIR, 2014c)
	Simmondsia Chinensis (Jojoba) Seed Oil	S	SC; V	(CIR, 2008c)
	Allantoin	S	SC; SP	(CIR, 2010a)
	Phenoxyethanol	S	F; P	(CIR, 2011a)
	Ethylhexylglycerin	S	DO; SC	(CIR, 2013)
	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	S	E; V	(CIR, 2017b)
	Sodium Hydroxide	S	DN; PH; BU	(CIR, 2016c)
10	**Silk**	S	SC	(CIR, 2016g)
	Vitamin C (L-ascorbic acid)	S	AO; F; PH; SC	(CIR, 2005c)
11	Oryza Sativa (Rice) Starch	S	BI; V	(CIR, 2006a)
	Silk (Serica) Powder	S	F; P	(CIR, 2016g)

	Silica	S	BU	(CIR, 2009b)
	Fragrance (Parfum)	NA	F	N/A
	Linalool	NA	F; DO	N/A
	Limonene	NA	F	N/A
	Geraniol	NA	F	N/A
	Coumarin	NA	F	N/A
	Citronellol	NA	F	N/A
	Citral	NA	F	N/A
	Gentiana Lutea Root Extract	NA	F; SC	N/A
	Quercus Robur Bark Extract	NA	AS	N/A
	Salvia Officinalis (Sage) Leaf Extract	NA	F; SC; SO	N/A
	Diatomaceous Earth (Solum Diatomeae)	NA	BU	N/A
12	Water	NA	SO	N/A
	Silk	S	SC	(CIR, 2016g)
	Vitamin C (Ascorbyl Glucoside)	S	AO; F; PH; SC	(CIR, 2005c)
	Sodium Anisate	NA	NR	N/A
	Rosehip Oil	S	SC	(CIR, 2017e)
13	Alcohol Certified Organic	NA	AM; F; SO; V	N/A
	Aloe Barbadensis (Aloe) Leaf Gel	S	SC	(CIR, 2007b)
	Apricot Oil	S	F; SC	(CIR, 2011c)
	Ascorbyl Palmitate	S	AO; F; V; SP	(CIR, 2017d)
	Coconut Oil	S	F; SC; SO	(CIR, 2011b)
	Glucose Oxidase	NA	SC	N/A
	Jasmine Sambac Oil	NA	NR	N/A
	Lactoperoxidase	NA	SC	N/A
	Milk And Sugar Enzymes	NA	SC	N/A
	Potassium Sorbate	S	F; P	(CIR, 2008a)
	Retinyl	S	SC	(CIR, 2008a)

	Rosa Damascena Oil	NA	F	N/A
	Safflower Seed Certified Organic Oil	S	F; SC	(CIR, 2016f)
	Sea Algae Extract	NA	NR	N/A
	Silk Extract	S	SC	(CIR, 2016g)
	Soft-Water	NA	SO	N/A
	Squalane	S	SC	(CIR, 2003a)
	Tahitian Gardenia Oil	NA	NR	N/A
	Tocopheryl Acetate	S	AO; SC	(CIR, 2014c)
	Vegetable Glycerin	S	F; SC; V	(CIR, 2015b)
	Vegetable-Derived Emulsifying Wax	S	E	(CIR, 2005b)
	White Wine And Japanese Plum Extract	NA	H	N/A
	Xanthan Gum	S	SC; SU; E; V	(CIR, 2016d)

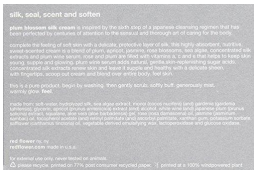
Table 44. Labeling Assessment (Rose-based Products)

Product Number	Label (Front)	Label (Back)	Labeling Assessment	Information Included on Website
1	Image Unavailable	Image Unavailable	Incomplete Packaging Assessment	Meets Requirements
2		Image Unavailable	Incomplete Packaging Assessment	Meets Requirements
3			Meets Requirements	N/A
4		Image Unavailable	Incomplete Packaging Assessment	Meets Requirements
5			Meets Requirements	N/A

6		Image Unavailable	Incomplete Packaging Assessment	Meets Requirements

Table 45. Labeling Assessment (Silk-based and Rose+Silk Combo Products)

Product Number	Label (Front)	Label (Back)	Labeling Assessment	Information Included on Website
7			Meets Requirements	N/A
8			Meets Requirements	N/A
9			Meets Requirements	N/A

10		Image Unavailable	Incomplete Packaging Assessment	Meets Requirements
11		Image Unavailable	Incomplete Packaging Assessment	Meets Requirements
12			Meets Requirements	N/A
13		Image Unavailable	Incomplete Packaging Assessment	Meets Requirements

References

Acure Organics. (2017). Rosehip oil. Retrieved March 20, 2017, from https://www.acureorganics.com/rosehip-oil.html

Ajazzuddin, M., Jeswani, G., & Jha, A. (2015). Nanocosmetics: Past, Present and Future Trends. *Recent Patents on Nanomedicine*, *5*(1), 3–11.

Altman, G. H., Diaz, F., Jakuba, C., Calabro, T., Horan, R. L., Chen, J., … Kaplan, D. L. (2003). Silk-based biomaterials. *Biomaterials*, *24*(3), 401–416.

Altman, G. H., Horan, R. L., Dow, R. L., Lind, R. M., & Haas, D. S. (2015, November 17). *9187538*. *US Patent*. USPTO. Retrieved from https://www.google.com/patents/US9187538

Beautylish. (2017). Retrieved March 12, 2017, from www.beautylish.com

Bilia, A. R., Guccione, C., Isacchi, B., Righeschi, C., Firenzuoli, F., & Bergonzi, M. C. (2014). Essential Oils Loaded in Nanosystems: A Developing Strategy for a Successful Therapeutic Approach. *Evidence-Based Complementary and Alternative Medicine: eCAM*, *2014*, 1–14.

Bioalternatives. (2016a). About us. Retrieved May 5, 2017, from https://www.bioalternatives.com/en/bioalternatives/

Bioalternatives. (2016b, December 21). Reconstructed skin useful to study anti-ageing effects of cosmetics. Retrieved May 5, 2017, from https://www.bioalternatives.com/en/reconstructed-skin-ageing/

Bioalternatives. (2017, June 7). Preclinical research CRO, in vitro bioassays - Bioalternatives. Retrieved August 13, 2017, from https://www.bioalternatives.com/en/

Biossance. (2017). Squalane + Vitamin C Rose Oil. Retrieved March 20, 2017, from https://biossance.com/products/squalane-vitamin-c-rose-oil

Bluemercury. (2017). Retrieved March 12, 2017, from https://bluemercury.com/

Bobbi Brown Cosmetics. (2017). Skin Clarifier No. 75. Retrieved March 20, 2017, from https://www.bobbibrowncosmetics.com/product/14015/45875/skincare/serumstreatments/skin-clarifier-no-75--pore-oil-control/ss17

Buzzfile. (2017). Retrieved March 15, 2017, from http://www.buzzfile.com/

Cao, G., Alessio, H. M., & Cutler, R. G. (1993). Oxygen-radical absorbance capacity assay for antioxidants. *Free Radical Biology and Medicine*, *14*(3), 303–311.

Caruso, A. (2015). *Statistics of U.S. Businesses Employment and Payroll Summary: 2012*. U.S. Census Bureau. Retrieved from https://www.census.gov/content/dam/Census/library/publications/2015/econ/g12-susb.pdf

Cheema, S. K., Gobin, A. S., Rhea, R., Lopez-Berestein, G., Newman, R. A., & Mathur, A. B. (2007). Silk fibroin mediated delivery of liposomal emodin to breast cancer cells. *International Journal of Pharmaceutics*, *341*(1-2), 221–229.

Chondrogianni, N., Kapeta, S., Chinou, I., Vassilatou, K., Papassideri, I., & Gonos, E. S. (2010). Anti-ageing and rejuvenating effects of quercetin. *Experimental Gerontology*, *45*(10), 763–771.

Chrubasik, C., Roufogalis, B. D., Müller-Ladner, U., & Chrubasik, S. (2008). A systematic review on the Rosa canina effect and efficacy profiles. *Phytotherapy Research: PTR*, *22*(6), 725–733.

CIR. (1985). *Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr193.pdf

CIR. (2003a). *Annual Review of Cosmetic Ingredient Safety Assessments--2001/2002*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR691.pdf

CIR. (2003b). *Final report on the safety assessment of stearoxy dimethicone, dimethicone, methicone, amino bispropyl dimethicone, aminopropyl dimethicone, amodimethicone, amodimethicone hydroxystearate, behenoxy dimethicone, C24-28 alkyl methicone, C30-45 alkyl methicone, C30-45 alkyl dimethicone, cetearyl methicone, cetyl dimethicone, dimethoxysilyl ethylenediaminopropyl dimethicone, hexyl methicone, hydroxypropyldimethicone, stearamidopropyl dimethicone, stearyl dimethicone, stearyl methicone, and vinyldimethicone*. Cosmetic Ingredients Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr307.pdf

CIR. (2003c). *Safety assessment of Salicylic Acid, Butyloctyl Salicylate, Calcium Salicylate, C12-15 Alkyl Salicylate, Capryloyl Salicylic Acid, Hexyldodecyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Magnesium Salicylate, MEA-*

Salicylate, Ethylhexyl Salicylate, Potassium Salicylate, Methyl Salicylate, Myristyl Salicylate, Sodium Salicylate, TEA-Salicylate, and Tridecyl Salicylate. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr302.pdf

CIR. (2005a). *Amended final report on the safety assessment of polyacrylamide and acrylamide residues in cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr342.pdf

CIR. (2005b). *Annual Review of Cosmetic Ingredient Safety Assessments--2002/2003*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PRN475.pdf

CIR. (2005c). *Final report of the safety assessment of L-Ascorbic Acid, Calcium Ascorbate, Magnesium Ascorbate, Magnesium Ascorbyl Phosphate, Sodium Ascorbate, and Sodium Ascorbyl Phosphate as used in cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr278.pdf

CIR. (2006a). *Amended final report on the safety assessment of Oryza Sativa (rice) Bran Oil, Oryza Sativa (rice) Germ Oil, Rice Bran Acid,Oryza Sativa (rice) Bran Wax, Hydrogenated Rice Bran Wax, Oryza Sativa (rice)Bran Extract, Oryza Sativa (rice) Extract, Oryza Sativa (rice) Germ Powder, Oryza Sativa (rice) Starch, Oryza Sativa (rice) Bran, Hydrolyzed Rice Bran Extract, Hydrolyzed Rice Bran Protein, Hydrolyzed Rice Extract, and Hydrolyzed Rice Protein*. Cosmetic Ingredient Review . Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr403.pdf

CIR. (2006b). *Annual review of cosmetic ingredient safety assessments-2004/2005*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PRN513.pdf

CIR. (2007a). *Amended final report on the safety assessment of glyceryl dilaurate, glyceryl diarachidate, glyceryl dibehenate, glyceryl dierucate, glyceryl dihydroxystearate, glyceryl diisopalmitate, glyceryl diisostearate, glyceryl dilinoleate, glyceryl dimyristate, glyceryl dioleate, glyceryl diricinoleate, glyceryl dipalmitate, glyceryl dipalmitoleate, glyceryl distearate, glyceryl palmitate lactate, glyceryl stearate citrate, glyceryl stearate lactate, and glyceryl stearate succinate*. Cosmetic Ingredient Review . Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR441.pdf

CIR. (2007b). *Final report on the safety assessment of AloeAndongensis Extract, Aloe Andongensis Leaf Juice,aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe*

Barbadensis Leaf, Aloe Barbadensis Leaf Extract, Aloe Barbadensis Leaf Juice,aloe Barbadensis Leaf Polysaccharides, Aloe Barbadensis Leaf Water, Aloe Ferox Leaf Extract, Aloe Ferox Leaf Juice, and Aloe Ferox Leaf Juice Extract. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr274.pdf

CIR. (2008a). *Annual Review of Cosmetic Ingredient Safety Assessments: 2005/2006*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/prn547.PDF

CIR. (2008b). *Final amended report on the safety assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in cosmetic products*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR427.pdf

CIR. (2008c). *Safety Assessment of Simmondsia Chinensis (Jojoba) Seed Oil, Simmondsia Chinensis (Jojoba) Seed Wax, Hydrogenated Jojoba Oil, Hydrolyzed Jojoba Esters, Isomerized Jojoba Oil, Jojoba Esters, Simmondsia Chinensis (Jojoba) Butter, Jojoba Alcohol, and Synthetic Jojoba Oil*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR525.pdf

CIR. (2009a). *Final report of the safety assessment of hyaluronic acid, potassium hyaluronate, and sodium hyaluronate*. Cosmetic Ingredient Review,. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr450.PDF

CIR. (2009b). *Safety Assessment of Silica and Related Cosmetic Ingredients*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR466.pdf

CIR. (2010a). *Final report of the safety assessment of allantoin and its related complexes*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR458.pdf

CIR. (2010b). *Final report on the safety assessment of sodium cetearyl sulfate and related alkyl sulfates as used in cosmetics*. Cosmetic Ingredient Review . Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR532.pdf

CIR. (2011a). *Annual Review of Cosmetic Ingredient Safety Assessments: 2007-2010*. Cosmetic Ingredient Review,. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR609.pdf

CIR. (2011b). *Final report on the safety assessment of Cocos nucifera (coconut) oil and*

related ingredients. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr507.pdf

CIR. (2011c). *Plant-Derived Fatty Acid Oils as Used in Cosmetics*. {Cosmetic Ingredient Review}. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR577.pdf

CIR. (2011d). *Safety assessment of cyclomethicone, cyclotetrasiloxane, cyclopentasiloxane, cyclohexasiloxane, and cycloheptasiloxane*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr497.pdf

CIR. (2012a). *Safety assessment of alkyl benzoates as used in cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr578.pdf

CIR. (2012b). *Safety assessment of alkyl PEG ethers as used in cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR581.PDF

CIR. (2012c). *Safety assessment of isoparaffins as used in cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr579.pdf

CIR. (2013). *Safety assessment of alkyl glyceryl ethers as used in cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR588.pdf

CIR. (2014a). *Safety Assessment of Alkyl Phosphates as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR671.pdf

CIR. (2014b). *Safety Assessment of Rosmarinus Officinalis (Rosemary)-Derived Ingredients as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR652.pdf

CIR. (2014c). *Safety Assessment of Tocopherols and Tocotrienols as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR667.pdf

CIR. (2015a). *Safety Assessment of Alkyl Esters as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR623.pdf

CIR. (2015b). *Safety Assessment of Glycerin as Used in Cosmetics*. Cosmetic Ingredient

Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR679.pdf

CIR. (2015c). *Safety Assessment of Polysorbates as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR696.pdf

CIR. (2016a). *Safety Assessment of Citrus Fruit-Derived Ingredients as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR691.pdf

CIR. (2016b). *Safety Assessment of Inorganic Hydroxides as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR703.pdf

CIR. (2016c). *Safety Assessment of Inorganic Hydroxides as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR703.pdf

CIR. (2016d). *Safety Assessment of Microbial Polysaccharide Gums as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR611.pdf

CIR. (2016e). *Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR706.pdf

CIR. (2016f). *Safety Assessment of Polyglyceryl Fatty Acid Esters as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR717.pdf

CIR. (2016g). *Safety Assessment of Silk Protein Ingredients as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from http://www.cir-safety.org/sites/default/files/slkprt122015rep.pdf

CIR. (2017a). *Safety Assessment of Butyrospermum parkii (Shea)- Derived Ingredients as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR720.pdf

CIR. (2017b). *Safety Assessment of Cross-Linked Alkyl Acrylates as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR583.pdf

CIR. (2017c). *Safety Assessment of Ethers and Esters of Ascorbic Acid as Used in*

Cosmetic. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR734.pdf

CIR. (2017d). *Safety Assessment of Ethers and Esters of Ascorbic Acid as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR734.pdf

CIR. (2017e). *Safety Assessment of Rosa canina-derived Ingredients as Used in Cosmetics*. Cosmetic Ingredient Review. Retrieved from https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR715.pdf

Contri, R. V., Kulkamp-Guerreiro, I. C., da Silva, S. J., Frank, L. A., Pohlmann, A. R., & Guterres, S. S. (2016). Nanoencapsulation of Rose-Hip Oil Prevents Oil Oxidation and Allows Obtainment of Gel and Film Topical Formulations. *AAPS PharmSciTech*, *17*(4), 863–871.

Cosmetic Ingredient Review. (2010a). About the Cosmetic Ingredient Review | Cosmetic Ingredient Review. Retrieved February 27, 2017, from https://www.cir-safety.org/about

Cosmetic Ingredient Review. (2010b). *Cosmetic Ingredient Review Procedures*. Retrieved from http://www.cir-safety.org/sites/default/files/pdf1.pdf

Dermstore. (2017). Retrieved March 11, 2017, from http://www.dermstore.com/

Dr. Hauschka. (2017). Silk Body Powder. Retrieved March 20, 2017, from https://www.dr.hauschka.com/en_US/natural-skin-care/silk-body-powder/

El-Domyati, M., Attia, S., Saleh, F., Brown, D., Birk, D. E., Gasparro, F., … Uitto, J. (2002). Intrinsic aging vs. photoaging: a comparative histopathological, immunohistochemical, and ultrastructural study of skin. *Experimental Dermatology*, *11*(5), 398–405.

Ercisli, S. (2007). Chemical composition of fruits in some rose (Rosa spp.) species. *Food Chemistry*, *104*(4), 1379–1384.

EWG. (2015, October). Retrieved March 20, 2017, from https://www.ewg.org/

EWG. (2017). Build Your Own Report. Retrieved March 22, 2017, from http://www.ewg.org/skindeep/tools/index.php

Fan, L., Wang, H., Zhang, K., Cai, Z., He, C., Sheng, X., & Mo, X. (2012). Vitamin C-reinforcing silk fibroin nanofibrous matrices for skin care application. *RSC Advances*, *2*(10), 4110.

Federal Trade Commission. (2013, December 12). Fair Packaging and Labeling Act. Retrieved February 25, 2017, from https://www.ftc.gov/enforcement/rules/rulemaking-regulatory-reform-proceedings/fair-packaging-labeling-act

Fiume MM, E. al. (n.d.). Safety assessment of propylene glycol, tripropylene glycol, and PPGs as used in cosmetics. - PubMed - NCBI. Retrieved November 10, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23064775

Google. (2017a). Retrieved March 10, 2017, from www.google.com

Google. (2017b). Google Patents. Retrieved March 13, 2017, from https://patents.google.com/

Green Beauty Barometer Survey. (2016). Retrieved February 10, 2017, from https://karigran.com/pages/greenbeauty

Gulrajani, M. L. (1988). Degumming of Silk. In *Silk Dyeing, Printing, and Finishing* (pp. 63–95).

Handoo, S., Arora, V., Khera, D., Nandi, P. K., & Sahu, S. K. (2012). A comprehensive study on regulatory requirements for development and filing of generic drugs globally. *International Journal of Pharmaceutical Investigation*, *2*(3), 99–105.

Heslot, H. (1998). Artificial fibrous proteins: A review. *Biochimie*, *80*(1), 19–31.

Ilyasoğlu, H. (2014). Characterization of Rosehip (Rosa canina L.) Seed and Seed Oil. *International Journal of Food Properties*, *17*(7), 1591–1598.

International Conference on Harmonisation. (2016). ICH Official web site : ICH. Retrieved February 17, 2017, from http://www.ich.org/home.html

Jergens. (2015, March 17). Jergens Daily Moisture Fragrance Free Dry Skin Moisturizer. Retrieved March 20, 2017, from http://www.jergens.com/products/daily-moisturizers/daily-moisture-fragrance-free-moisturizer.aspx

Kılıçgün, H., & Altıner, D. (2010). Correlation between antioxidant effect mechanisms and polyphenol content of Rosa canina. *Pharmacognosy Magazine*, *6*(23), 238–241.

Kligman, A. (2006). The Future of Cosmeceuticals: An Interview with Albert Kligman, MD, PhD. *Dermatol. Surg.* https://doi.org/10.1111/j.1524-4725.2005.31737

Kligman, A. M., Grove, G. L., Hirose, R., & Leyden, J. J. (1986). Topical tretinoin for

photoaged skin. *Journal of the American Academy of Dermatology*, *15*(4), 836–859.

Kligman, D. (2000). Cosmeceuticals. *Dermatologic Clinics*, *18*(4), 609–615.

Kundu, J., Chung, Y.-I., Kim, Y. H., Tae, G., & Kundu, S. C. (2010). Silk fibroin nanoparticles for cellular uptake and control release. *International Journal of Pharmaceutics*, *388*(1-2), 242–250.

Larsen, E., Kharazmi, A., Christensen, L. P., & Christensen, S. B. (2003). An antiinflammatory galactolipid from rose hip (Rosa canina) that inhibits chemotaxis of human peripheral blood neutrophils in vitro. *Journal of Natural Products*, *66*(7), 994–995.

Lattanzio, F., Greco, E., Carretta, D., Cervellati, R., Govoni, P., & Speroni, E. (2011). In vivo anti-inflammatory effect of Rosa canina L. extract. *Journal of Ethnopharmacology*, *137*(1), 880–885.

LinkedIn. (2017). Retrieved March 15, 2017, from www.linkedin.com

Liu, X.-Y., Zhang, C.-C., Xu, W.-L., & Ouyang, C.-X. (2009). Controlled release of heparin from blended polyurethane and silk fibroin film. *Materials Letters*, *63*(2), 263–265.

Lorencini, M., Brohem, C. A., Dieamant, G. C., Zanchin, N. I. T., & Maibach, H. I. (2014). Active ingredients against human epidermal aging. *Ageing Research Reviews*, *15*, 100–115.

Meinel, L., Hofmann, S., Karageorgiou, V., Kirker-Head, C., McCool, J., Gronowicz, G., … Kaplan, D. L. (2005). The inflammatory responses to silk films in vitro and in vivo. *Biomaterials*, *26*(2), 147–155.

Mondal, M., Trivedy, K., & Nirmal Kumar, S. (2006). The silk proteins, sericin and fibroin in silkworm, Bombyx mori Linn. - A review. *Caspian Journal of Environmental. Sciences*, *5*(2).

Murphy, A. R., & Kaplan, D. L. (2009). Biomedical applications of chemically-modified silk fibroin. *Journal of Materials Chemistry*, *19*(36), 6443–6450.

Nađpal, J. D., Lesjak, M. M., Šibul, F. S., Anačkov, G. T., Četojević-Simin, D. D., Mimica-Dukić, N. M., & Beara, I. N. (2016). Comparative study of biological activities and phytochemical composition of two rose hips and their preserves: Rosa canina L. and Rosa arvensis Huds. *Food Chemistry*, *192*, 907–914.

National Cancer Institute. (2016). Nanotechnology Characterization Laboratory (NCL).

Retrieved February 23, 2017, from https://ncl.cancer.gov/

National Center for Biotechnology Information. (2017). PubMed. Retrieved March 10, 2017, from https://www.ncbi.nlm.nih.gov/pubmed/

National Institute of Health. (2017). TOXNET. Retrieved March 5, 2017, from https://toxnet.nlm.nih.gov/

National Institutes of Health. (2017a). National Institutes of Health (NIH). Retrieved March 20, 2017, from https://www.nih.gov/

National Institutes of Health. (2017b). NIH Clinical Research Trials and You. Retrieved March 5, 2017, from https://clinicaltrials.gov/

Nikitakis, J., & Breslawec, H. P. (2014). *International Cosmetic Ingredient Dictionary and Handbook* (14th ed.). Washington DC: {Personal Care Products Council}.

Nohynek, G. J., & Dufour, E. K. (2012). Nano-sized cosmetic formulations or solid nanoparticles in sunscreens: a risk to human health? *Archives of Toxicology*, *86*(7), 1063–1075.

Odacite. (2017). Ro+Y. Retrieved March 20, 2017, from https://odacite.com/products/rosehip-ylang-ylang-serum-concentrate

Ofra Cosmetics. (2017). Peptide Silk-C Serum. Retrieved March 20, 2017, from https://www.ofracosmetics.com/products/ofra-peptide-silk-c-serum

Ozcan, M. (2002). Nutrient composition of rose (Rosa canina L.) seed and oils. *Journal of Medicinal Food*, *5*(3), 137–140.

Panilaitis, B., Altman, G. H., Chen, J., Jin, H. J., Karageorgiou, V., & Kaplan, D. L. (2003). Macrophage responses to silk. *Biomaterials*, *24*(18), 3079–3085.

PCA Skin. (2017). Silkcoat Balm. Retrieved March 20, 2017, from https://www.pcaskin.com/silkcoatr-balm.html

Personal Care Products Council. (2016). What is INCI? | Personal Care Products Council. Retrieved February 25, 2017, from http://www.personalcarecouncil.org/public/what-inci

Project on Emerging Nanotechnologies. (2013). Consumer Products Inventory. Retrieved February 20, 2017, from http://www.nanotechproject.org/cpi

Pubchem. (2017). Linolenic acid. Retrieved February 12, 2017, from

https://pubchem.ncbi.nlm.nih.gov/compound/5280934

Pugh, S. (1991). *Total Design: Integrated Methods for Successful Product Engineering*. Addison-Wesley.

Puizina-Ivić, N. (2008). Skin aging. *Acta Dermatovenerologica Alpina, Pannonica, et Adriatica*, *17*(2), 47–54.

Red Flower. (2017). plum blossom silk cream. Retrieved March 20, 2017, from https://redflower.com/plum-blossom-silk-cream.html

Reed, R. E. (1962). The definition of "cosmeceutical." *Journal of the Society of Cosmetic Chemists*, *13*(0), 103–106.

Robichaud, C. O., Tanzil, D., Weilenmann, U., & Wiesner, M. R. (2005). Relative risk analysis of several manufactured nanomaterials: an insurance industry context. *Environmental Science & Technology*, *39*(22), 8985–8994.

Rockwood, D. N., Preda, R. C., Yücel, T., Wang, X., Lovett, M. L., & Kaplan, D. L. (2011). Materials fabrication from Bombyx mori silk fibroin. *Nature Protocols*, *6*(10), 1612–1631.

Schwager, J., Hoeller, U., Wolfram, S., & Richard, N. (2011). Rose hip and its constituent galactolipids confer cartilage protection by modulating cytokine, and chemokine expression. *BMC Complementary and Alternative Medicine*, *11*, 105.

Sephora. (2017). Retrieved March 11, 2017, from www.sephora.com

Sheng, X., Fan, L., He, C., Zhang, K., Mo, X., & Wang, H. (2013). Vitamin E-loaded silk fibroin nanofibrous mats fabricated by green process for skin care application. *International Journal of Biological Macromolecules*, *56*, 49–56.

Silab. (2017). SEBOCYTINE®. Retrieved March 20, 2017, from http://www.silab.fr/produit-95-sebocytine_usa.html

Silk Therapeutics. (2017a). Clinical-Grade, Anti-Aging Skincare | Silk Therapeutics and LabGrab. Retrieved February 14, 2017, from https://silktherapeutics.com/

Silk Therapeutics. (2017b). Purely Smooth. Retrieved March 20, 2017, from https://silktherapeutics.com/products/purely-smooth

Silk Therapeutics. (2017c). Silk + C30 Film. Retrieved March 20, 2017, from https://silktherapeutics.com/products/silk-c30-film

Silk Therapeutics®. (2016, January 22). Silk Smoothing Complex: Clean, Powerful Anti-Aging. No Goop. Retrieved February 13, 2017, from https://silktherapeutics.com/blogs/silk-unraveled/silk-smoothing-complex-clean-powerful-anti-aging-no-goop

Skin Deep® Cosmetics Database. (2017a). Retrieved March 20, 2017, from https://www.ewg.org/skindeep/

Skin Deep® Cosmetics Database. (2017b). Retrieved March 20, 2017, from https://www.ewg.org/skindeep/site/about.php#.Wf3wGBNSxSw

SkinStore. (2017). Retrieved March 11, 2017, from https://www.skinstore.com/

Szentmihályi, K., Vinkler, P., Lakatos, B., Illés, V., & Then, M. (2002). Rose hip (Rosa canina L.) oil obtained from waste hip seeds by different extraction methods. *Bioresource Technology*, *82*(2), 195–201.

Thayer, J. D. (2005). The SPS Agreement: Can It Regulate Trade in Nanotechnology? *Duke Law & Technology Review*, (15). Retrieved from http://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1135&context=dltr

The Detox Market. (2017). Retrieved March 12, 2017, from www.detoxmarket.com

Think Dirty. (2012). Think Dirty App. Retrieved June 12, 2017, from https://www.thinkdirtyapp.com/about-methodology.php

Think Dirty. (2015). Think Dirty App. Retrieved June 12, 2017, from https://www.thinkdirtyapp.com/

Ulta Beauty. (2017). Retrieved March 11, 2017, from www.ulta.com

United States Patent and Trademark Office. (1994, December 1). United States Patent and Trademark Office. Retrieved March 17, 2017, from https://www.uspto.gov/

United States Patent and Trademark Office. (2009, July 4). Search for patents. Retrieved March 23, 2017, from https://www.uspto.gov/patents-application-process/search-patents

United States Pharmacopeial. (2016). United States Pharmacopeial. Retrieved February 20, 2017, from http://www.usp.org/

U.S. Food & Drug Administration. (2006, August 9). *FDA Forms Internal Nanotechnology Task Force*. Retrieved from https://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4241B1-02-33-FDA-

Nano%20FDA%20News%20release.pdf

U.S. Food & Drug Administration. (2007). *Nanotechnology - Nanotechnology Task Force Report 2007*. Retrieved from https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm2006659.htm

U.S. Food & Drug Administration. (2012, April 30). Laws & Regulations - Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?). Retrieved February, 17, 2017, from https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074201.htm

U.S. Food & Drug Administration. (2013a). Nanotechnology - 2013 Nanotechnology Regulatory Science Research Plan. Retrieved February 25, 2017, from https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm273325.htm

U.S. Food & Drug Administration. (2013b, August 3). Laws & Regulations - FDA Authority Over Cosmetics: How Cosmetics Are Not FDA-Approved, but Are FDA-Regulated. Retrieved November 2, 2017, from http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074162.htm

U.S. Food & Drug Administration. (2014a, June). Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology. Retrieved February 25, 2017, from https://www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm

U.S. Food & Drug Administration. (2014b, June 30). Guidance Documents - Guidance for Industry: Safety of Nanomaterials in Cosmetic Products. Retrieved February 23, 2017, from https://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm300886.htm

U.S. Food & Drug Administration. (2015a, February 27). Nanotechnology - Nanotechnology Task Force. Retrieved February 20, 2017, from http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm2006658.htm

U.S. Food & Drug Administration. (2015b, August 24). FDA's Drug Review Process: Continued. Retrieved February 21, 2017, from http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm289601.htm

U.S. Food & Drug Administration. (2016, December 6). FDA Basics - How FDA Evaluates Regulated Products: Cosmetics. Retrieved February 12, 2017, from

http://www.fda.gov/AboutFDA/Transparency/Basics/ucm262353.htm

U.S. Food & Drug Administration. (2017a). Labeling Regulations - Cosmetic Labeling Guide. Retrieved February 8, 2017, from https://www.fda.gov/Cosmetics/Labeling/Regulations/ucm126444.htm

U.S. Food & Drug Administration. (2017b, November 3). Warning Letters - Warning Letters Address Drug Claims Made for Products Marketed as Cosmetics. Retrieved November 10, 2017, from http://www.fda.gov/Cosmetics/ComplianceEnforcement/WarningLetters/ucm081086.htm

Valerón-Almazán, P., Gómez-Duaso, A. J., Santana-Molina, N., García-Bello, M. A., & Carretero, G. (2015). Evolution of Post-Surgical Scars Treated with Pure Rosehip Seed Oil. *Journal of Cosmetics, Dermatological Sciences and Applications*, *05*(02), 161–167.

Vance, M. E., Kuiken, T., Vejerano, E. P., McGinnis, S. P., Hochella, M. F., Jr, Rejeski, D., & Hull, M. S. (2015). Nanotechnology in the real world: Redeveloping the nanomaterial consumer products inventory. *Beilstein Journal of Nanotechnology*, *6*, 1769–1780.

Wayner, D. D., Burton, G. W., Ingold, K. U., & Locke, S. (1985). Quantitative measurement of the total, peroxyl radical-trapping antioxidant capability of human blood plasma by controlled peroxidation. The important contribution made by plasma proteins. *FEBS Letters*, *187*(1), 33–37.

Wenzig, E. M., Widowitz, U., Kunert, O., Chrubasik, S., Bucar, F., Knauder, E., & Bauer, R. (2008). Phytochemical composition and in vitro pharmacological activity of two rose hip (Rosa canina L.) preparations. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology*, *15*(10), 826–835.

Wilczewska, A. Z., Niemirowicz, K., Markiewicz, K. H., & Car, H. (2012). Nanoparticles as drug delivery systems. *Pharmacological Reports: PR*, *64*(5), 1020–1037.

Wilson, R. F. (2006). Nanotechnology: the challenge of regulating known unknowns. *The Journal of Law, Medicine & Ethics: A Journal of the American Society of Law, Medicine & Ethics*, *34*(4), 704–713.

Winther, K., Campbell-Tofte, J., & Hansen, A. S. V. (2016). Bioactive ingredients of rose hips (Rosa canina L) with special reference to antioxidative and anti-inflammatory properties: in vitro studies. *Botanics: Targets and Therapy*, 11.

WIPO. (2017). World Intellectual Property Organization (WIPO). Retrieved March 20, 2017, from https://patentscope.wipo.int/search/en/search.jsf

Wongpinyochit, T., Johnston, B. F., & Seib, F. P. (2016). Manufacture and Drug Delivery Applications of Silk Nanoparticles. *Journal of Visualized Experiments: JoVE*, (116). https://doi.org/10.3791/54669

Xia, Y., Yang, P., Sun, Y., Wu, Y., Mayers, B., Gates, B., … Yan, H. (2003). One-Dimensional Nanostructures: Synthesis, Characterization, and Applications. *ChemInform*, *34*(22). https://doi.org/10.1002/chin.200322236

Zhang, X., Tsukada, M., Morikawa, H., Aojima, K., Zhang, G., & Miura, M. (2011). Production of silk sericin/silk fibroin blend nanofibers. *Nanoscale Research Letters*, *6*, 510.

Zhou, C. Z., Confalonieri, F., Medina, N., Zivanovic, Y., Esnault, C., Yang, T., … Li, Z. G. (2000). Fine organization of Bombyx mori fibroin heavy chain gene. *Nucleic Acids Research*, *28*(12), 2413–2419.

Zlatanov, M. D. (1999). Lipid composition of Bulgarian chokeberry, black currant and rose hip seed oils. *Journal of the Science of Food and Agriculture*, *79*(12), 1620–1624.